

Undifferentiated Small Cell Carcinoma of the Uterine Cervix Effectively Treated with Chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine) and Whole Brain Irradiation

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A 42-year-old woman had stage IV undifferentiated small cell carcinoma of the uterine cervix with metastasis to the brain, liver, adrenal gland, pelvic lymph nodes, superficial lymph nodes, and skin. She was treated with whole brain irradiation and systemic chemotherapy consisting of cyclophosphamide, doxorubicin (Adriamycin; Pharmacia, Dublin, OH, USA) and vincristine. After completion of radiation therapy and 1 course of chemotherapy, there was no radiographic evidence of metastatic lesions, nor macroscopic or histologic evidence of the primary cervical lesion.

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INTRODUCTION

Undifferentiated small cell carcinoma is rare, accounting for only 1.1% to 3.2% of cases of cervical cancer.^{1,2} Tateishi et al.³ presented the first reported cases, 5 patients with argyrophil cell carcinoma of the uterine cervix, in 1975. This tumor behaves aggressively, with early systemic metastasis and a poor prognosis. In patients with stage I disease, the 5-year survival rate is about 50%.¹ When the disease is at stage II or more, the prognosis is dismal, with a 5-year survival rate around 10%. Because this tumor spreads extensively, effective chemotherapy is needed. We report the case of a patient who had extensive metastatic lesions that responded well to a combination of chemotherapy and radiation therapy.

CASE REPORT

The patient was a 42-year-old woman (gravida II, para II). The results of a routine cervical smear in October 1995 suggested the presence of malignant cells, although the patient was asymptomatic and the cervix appeared macroscopically normal. The patient did not return at that time for further testing. In February 1996, she

noticed right neck lymph node swelling and visited a local physician. Histologic analysis of a biopsy sample from the lymph node revealed poorly differentiated carcinoma. An evaluation for metastasis revealed multiple lesions involving the brain, liver, adrenal gland, bilateral neck lymph nodes, bilateral axillar lymph nodes, and skin.

In April 1996 she returned to our department because of persistent atypical genital bleeding. Speculum examination revealed that the anterior lip of the uterine cervix had been replaced by cancerous tissue and that there was a downward displacement of the cervix. A bimanual examination revealed a hard cervical mass 6 cm in diameter extending to both pelvic sidewalls. Computed tomography (CT) showed that the cervix was enlarged to about 6 cm and that the bilateral pelvic lymph nodes probably were swollen. Histologic examination of the tumor showed predominantly small cells exhibiting sparse cytoplasm, infiltrative growth in the surrounding tissues, and necrosis. The nuclei of these cells contained abundant chromatin, and some had small nucleoli (Fig. 1). An immunohistochemical study showed a positive reaction to epithelial membrane antigen, but a negative reaction to lymphocyte common antigen, keratin, S-100 protein, and chromogranin. Other laboratory results included elevated levels of common antigen CA12-5 (125 U/mL) and neuron-specific enolase (31.7 ng/mL), but normal values of progastrin-releasing peptide, adrenocorticotrophic hormone, and cortisol. These results indicated stage IVb

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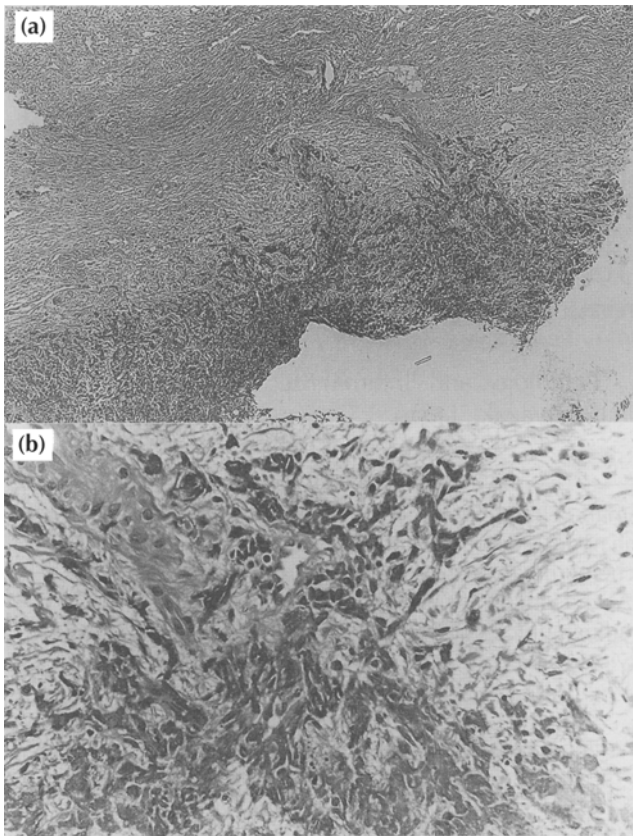


Fig. 1. Tumor cells of undifferentiated small cell carcinoma of the uterine cervix of a 42-year-old woman (gravida II, para II) with right neck lymph node swelling and persistent atypical genital bleeding. (a) The cells are small with sparse cytoplasm. The tumor infiltrates diffusely. H&E; original magnification, $\times 15$. (b) The cells have small nuclei with fine rich chromatin and occasional small nucleoli. H&E; original magnification, $\times 60$.

undifferentiated small cell carcinoma of the uterine cervix.

The patient was admitted to our hospital for treatment. She began radiation therapy to the whole brain for metastatic brain tumor with concomitant administration of dexamethasone. The radiation dose was 1.5 Gy per fraction, 5 fractions per week, to a total of 45 Gy. Simultaneously, cyclophosphamide (750 mg/m^2), doxorubicin (Adriamycin; Pharmacia, Dublin, OH, USA) (50 mg/m^2), and vincristine (1 mg/m^2) (CAV) therapy was begun because of extensive systemic disease. During chemotherapy, the patient experienced grade 3 nausea and vomiting (maximal daily number of episodes of emesis > 6) and grade 4 leukocytopenia (minimal number of leukocytes, 600), according to the toxicity grading criteria of the Japan Clinical Oncology Group.⁴

After completion of radiation therapy and 1 course of chemotherapy, metastatic lesions completely disappeared, as confirmed by physical and radiographic examinations (Figs. 2, 3). Speculum and bimanual examinations showed that the cervix also was negative for

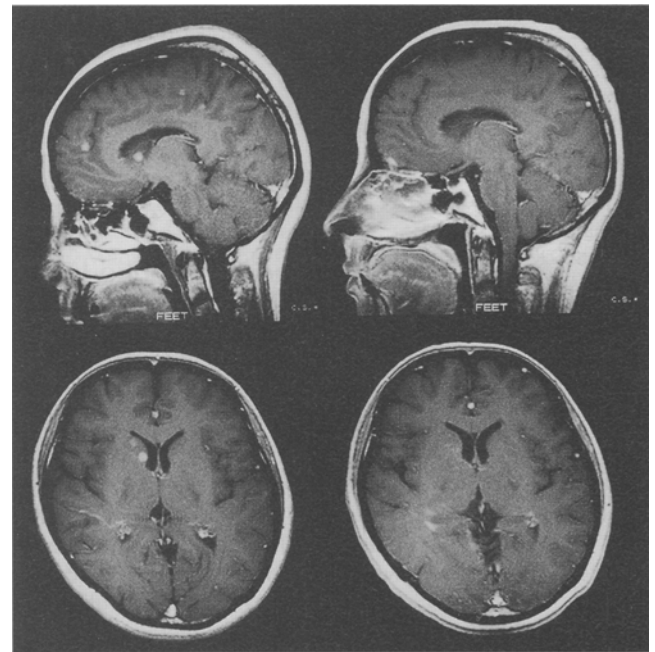


Fig. 2. Magnetic resonance imaging of the brain of the patient described in Fig. 1, taken before whole brain irradiation. Multiple brain metastases are evident (left). After intracranial irradiation, these tumors are gone (right).

the existence of tumor (Fig. 4). CT showed remarkable shrinkage of cervical size and disappearance of the bilateral pelvic nodes (Fig. 5). The results of multiple random biopsy of the anterior lip of the cervix confirmed that no residual tumor existed.

Three months after the start of therapy and after 4 courses of chemotherapy the patient remains free of disease. The patient will next receive high-dose chemotherapy supported by infusion of peripheral blood stem cells.

DISCUSSION

Undifferentiated small cell carcinoma of the uterine cervix is rare.¹ In our hospital, 727 uterine cervical cancer cases were seen in the past 13 years; of these, only 4 (0.55%) were small cell carcinoma. The clinical course of small cell carcinoma is usually very rapid, and the prognosis is dismal, with a 5-year survival rate of 50%, even in stage I carcinoma.^{1,2,5}

Immunohistochemical staining is helpful in diag-

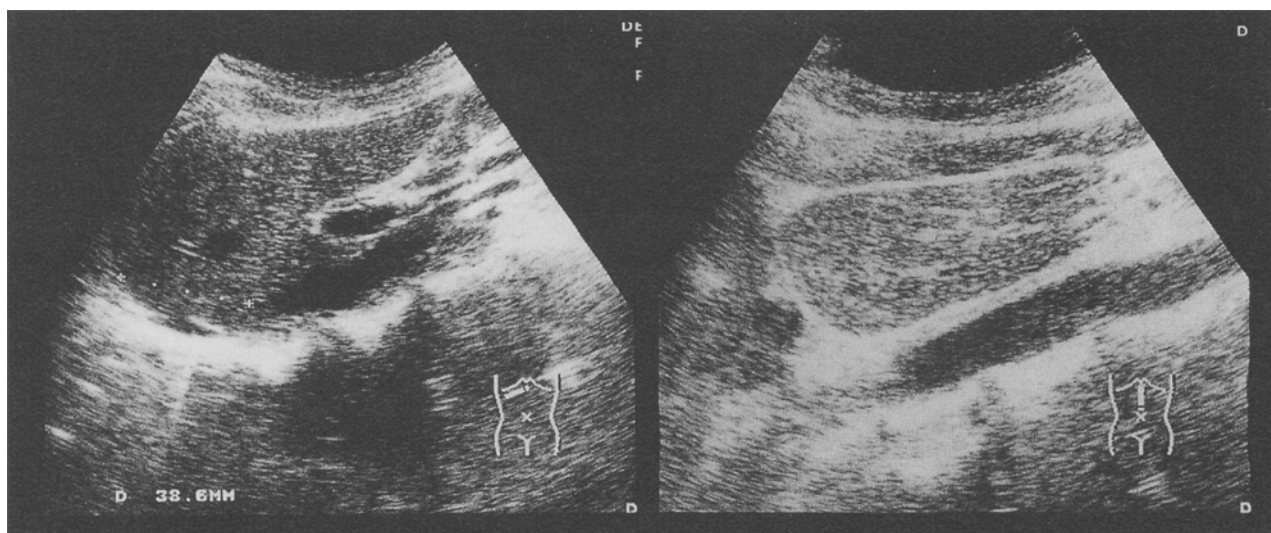


Fig. 3. Ultrasonography of the liver of the patient described in Fig. 1, taken before chemotherapy. A space-occupying lesion is found in the S2 region of the liver (left). After chemotherapy, the lesion has completely disappeared (right).

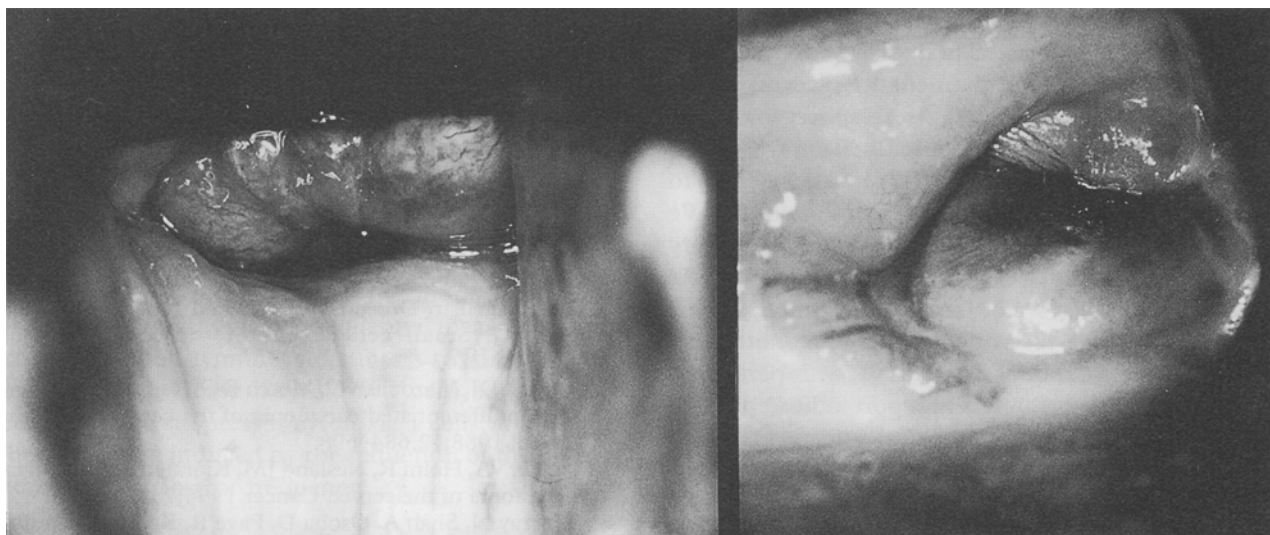


Fig. 4. Colposcopic examination showing that the anterior lip of the cervix of the patient described in Fig. 1 has been replaced by visible tumor (left). After chemotherapy, the anterior lip looks macroscopically normal (right), as confirmed by negative histologic findings.

nosing this type of tumor. Neuroendocrine and epithelial differentiation are evident in most tumors.^{2,5-7} In particular, elevated levels of chromogranin, synaptophysin, and neuron-specific enolase frequently occur.^{6,7} In our patient, epithelial marker was present in the tumor cells, but chromogranin was not. Although neuron-specific enolase and synaptophysin levels were not assessed, the typical histologic findings and aggressive clinical features of our case study indicated undifferentiated small cell carcinoma.^{5,7}

Undifferentiated small cell cervical cancer is difficult to treat with surgery or radiation. Its prognosis appears to be worse than that of other types of cervical

cancers.⁵ Frequently, local lymph node metastases and vascular space involvement occur even in early stage disease.^{1,2,5} Distant metastasis is also frequently observed, especially in the lymph nodes, lungs, brain, and liver.⁵⁻⁷ Therefore, effective systemic treatment is needed to improve survival. For brain metastasis, whole brain irradiation is the treatment of choice to control intracranial lesions because of the blood brain barrier to chemotherapeutic agents. Various kinds of chemotherapeutic drugs have been used.^{6,7}

Recently, neoadjuvant or postoperative chemotherapy (cisplatin, doxorubicin, and etoposide, or cisplatin and etoposide) have been used in an attempt to improve

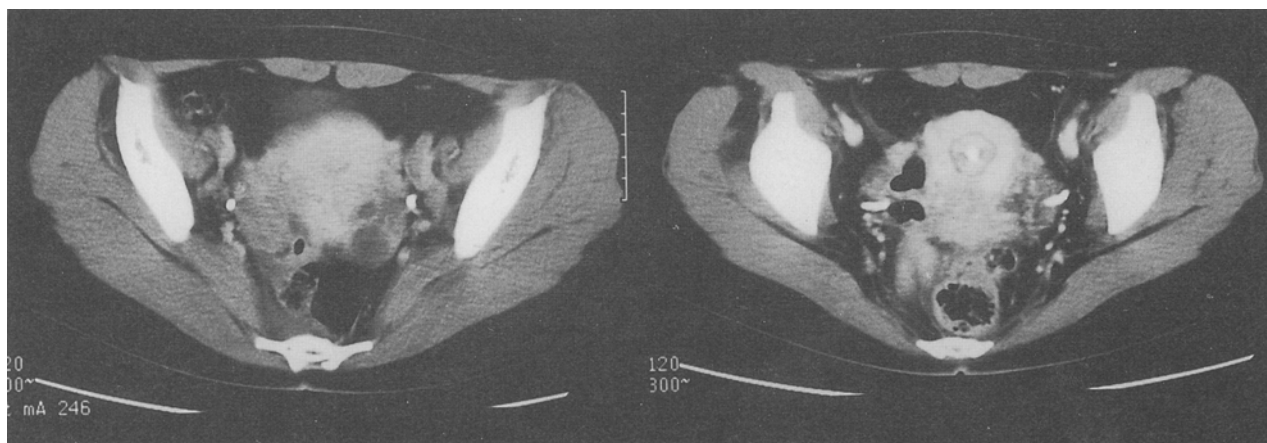


Fig. 5. Computed tomography of the pelvis of the patient described in Fig. 1, taken before chemotherapy. A 6-cm cervical mass is detected, along with bilateral pelvic lymphadenopathy (left). After chemotherapy, the cervix is remarkably decreased in size, and bilateral pelvic lymphadenopathy has disappeared (right).

survival.⁸⁻¹⁰ A high response rate (5/7, 71%) was reported in cases of advanced disease,⁹ and adjuvant chemotherapy was suggested to improve survival, compared with conventional treatment.⁹ However, in patients with extensive disease, complete response to chemotherapy was induced, but response duration was short, lasting only 1 year.¹¹ Further studies are needed to discover optimal chemotherapeutic combinations. We selected a CAV regimen, as it is known to be very effective in treating small cell carcinoma of the lung.¹⁰ As our patient responded well to the CAV regimen, we feel that it is worthwhile to try a high-dose chemotherapy regimen, and/or total body irradiation, with peripheral blood stem cell support. A recent report indicated a high response to and prolonged survival after a cisplatin, etoposide, doxorubicin, and vincristine regimen.⁹⁻¹¹ Our patient has shown that CAV also can be quite an effective regimen and is worth further study.

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