

Case Report

Cerebral metastasis of cervical cancer, report of two cases and review of the literature

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Abstract: Cervical cancers spread locally through the angiolymphatic apparatus and very rarely metastasize to the brain. The intracranial metastasis is a late event and a sign of poor prognosis. We present two cases of uterine cervical carcinomas with brain metastasis presenting with severe headaches in one case and hemiparesis and aphasia in the other one. Palliative craniotomy and debulking of the tumor was performed in both patients.

Keywords: Cervical cancer, brain metastases, carcinoma of uterine cervix, intracranial metastasis, metastatic cervical cancer

Introduction

Worldwide cervical cancer is the second most common malignancy among women. It usually spreads by local extension and through the lymphatics to the retroperitoneal lymph nodes. Distant, hematogenous metastases occur in 12% of the cases with the common sites including liver, lung, and bone. Metastases to the central nervous system are extremely rare, usually seen late in the course of the disease, and have poor prognosis. We report two rare cases of carcinoma of the cervix with metastases to brain and describe the histopathological features of the lesions and review of the literature.

Material and methods

The following two cases were evaluated and reported in accordance with the University of South Florida Institutional Review Board's policy #311.

Case 1

A 53 year-old female diagnosed with cervical cancer was transferred to our center with a sudden-onset right-side hemiparesis and aphasia. History of patient was significant for vaginal

bleedings during the past 5 years with no medical interventions. CT urogram of the abdomen and pelvis showed a large mass in the pelvis with possible necrosis, measuring about 12 cm involving the cervix and uterine body. There was extensive involvement of the vagina and probable invasion of the posterior bladder wall. She had an intraluminal filling defect in the right internal iliac vein.

Endometrial, endocervical, and lateral vaginal wall biopsy showed fragments of poorly differentiated carcinoma with squamous differentiation and malignant glandular epithelium in a background of extensive necrosis. Immunohistochemical study revealed the tumor cells are immunoreactive for CK5/6, CAM 5.2, p63, p16 and polyclonal CEA. They were negative for CK7, CK20, monoclonal CEA, CA-125, and thrombomodulin.

Staging radiology work-ups showed disseminated metastatic cancer with spread to liver, lungs, and brain. Brain MRI revealed multifocal intracranial lesions with extensive surrounding vasogenic edema and a left to right midline shift (**Figure 1**).

The patient then underwent craniotomy and debulking of the large left parietal lesion to

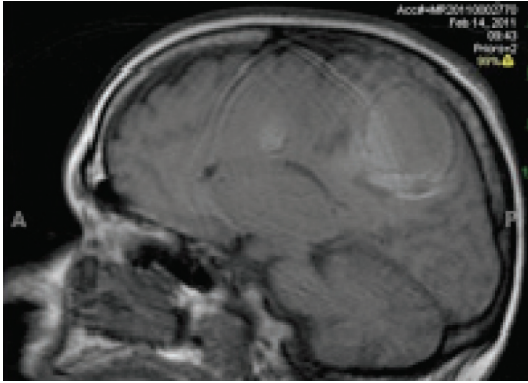


Figure 1. Case 1, MRI of the brain. A 4.0 cm space occupying lesion in the parieto-occipital region (arrow) is the largest intracranial metastasis.

reduce the mass effect. Histological examination of the brain mass revealed poorly differentiated carcinoma with features of glandular and squamous differentiation, infiltrating the brain parenchyma and consistent with metastasis from the primary cervical cancer.

Immunohistochemistry studies revealed immunoreactivity of tumor cells for polyclonal CEA, P16, and P63, confirming the diagnosis (**Figure 2**).

In her hospital course the patient progressively became unresponsive and expired due to multiple cerebral hemorrhages.

Case 2

A 43-year-old female presented with vaginal bleeding. On the exam the patient was noted to have a 10-cm cervical mass that invaded parametrium. Also, on the PET/CT it was shown there was hydronephrosis at the right side. For that reason, a right stent and ureteral drainage tube was placed. PET scan showed hypermetabolic areas in her lungs and her trochanteric area at right femur as less as less in the left paraspinal muscle.

The patient subsequently developed a severe headache over several days and was evaluated at our Cancer Center. The MRI showed Multiple intracranial metastases above the tentorium in both hemispheres with the largest, ring-enhancing cystic lesion with surrounding vasogenic edema and considerable mass effect located in the right frontal lobe measuring 5.1 cm x 4.0

cm. The second largest lesion was in the occipital pole on the right side measuring 2.04 cm x 3.6 cm. It also has vasogenic edema surrounding it.

The patient underwent a right frontal craniotomy for resection of tumor using micro-dissection technique under stereotactic guidance. A second procedure was performed and consisted of a parietal occipital craniotomy for resection of the tumor. She then completed whole cranial radiation.

The histologic evaluation of the specimen showed brain tissue involvement by metastatic poorly differentiated squamous cell carcinoma of cervical origin with focal neuroendocrine differentiation (**Figure 3A, B**). Marked mitotic figures including multiple atypical mitoses, as well as focal necrosis were identified. Immunostains with appropriate controls were performed which revealed immunoreactivity of the tumor cells for pancytokeratin, CAM 5.2 and p16 (**Figure 3C**). Focal nuclear reactivity with p63 was also evident. The proliferation index of Ki-67 is very high, more than 90%. In addition, the tumor cells are also positive for neuroendocrine markers of CD56 and synaptophysin (**Figure 3D**), focally positive for chromogranin, and negative for TTF-1, supporting the neuroendocrine differentiation. Patient received whole brain radiation and chemotherapy with Taxol/cisplatin.

Result and discussion

Cervical cancer is a major malignancy of female genital tract and usually spreads to the adjacent organs, and pelvic and para-aortic lymph nodes. Human Papilloma Virus (HPV) DNA can be detected in 90% to 100% all premalignant and malignant lesions of cervical mucosa and it is now a well-known fact that the HPV is the etiologic agent in these neoplasms [1-4]. p16 (INK4A) protein, a surrogate marker for high risk HPV DNA, is diffusely overexpressed in virtually all cases of cervical squamous cell carcinoma and endocervical adenocarcinoma and very rarely might be even detected focally in benign squamous and glandular mucosa [5, 6].

Overall brain metastasis occurs in 20-40% of cancer patients [7]. From the neurosurgery and neuropathology standpoints metastasis is the most common intracranial malignancy in adults

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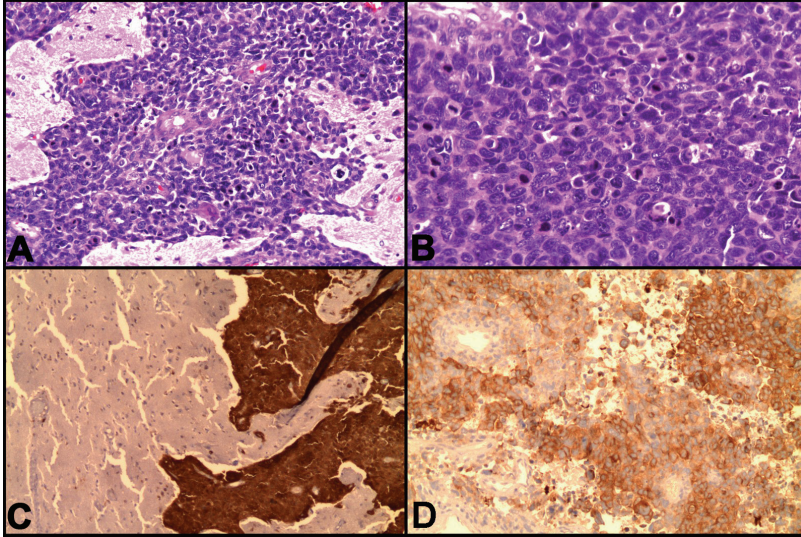


Figure 2. Case 1, Pathology. Poorly differentiated carcinoma with features of glandular and squamous differentiation, infiltrating the brain parenchyma. A: H&E (low power). B: H&E (higher power). C: p53 immunostain. D: p-CEA stain.

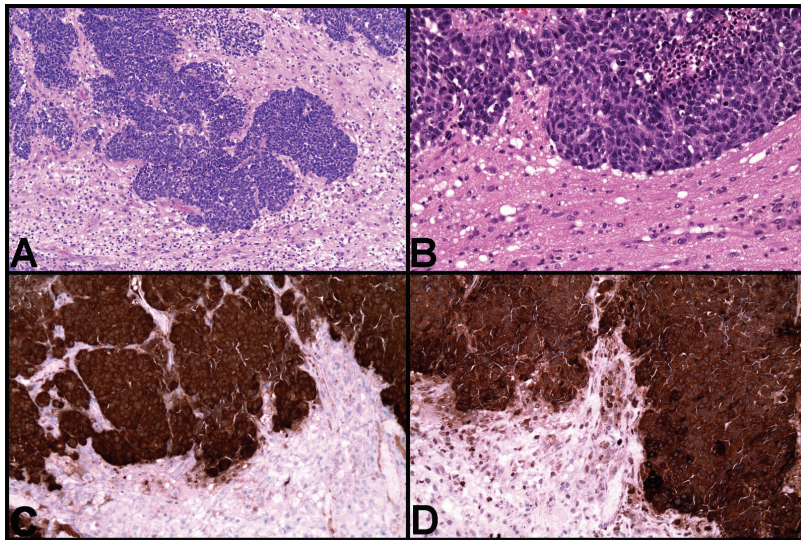


Figure 3. Case 2, Pathology. Brain tissue involvement by poorly differentiated squamous cell carcinoma. A: H&E (low power). B: H&E (higher power). C: p16 immunostain. D: Synaptophysin stain revealing neuroendocrine differentiation.

with the liver, lung, and bone tumors representing the most common sources. Other responsible tumors include breast, melanoma, colorectal, kidney, and thyroid primaries. Gynecologic malignancies rarely metastasize to brain and in this group choriocarcinoma is the one that most frequently metastasizes to the brain [8]. Cervical carcinomas are among the least common primary sites for cerebral spread.

based on regional blood flow within the brain. Although in some studies the location of the brain metastases was variable and there was no predilection for any anatomic site [12], our two cases show propensity of the metastatic lesions to supratentorial region as reported in more than 80% of brain metastases in other reported cases with cervical carcinoma [10, 11, 14].

Cervical carcinoma spreads locally through lymphatic vessels and hematogenous spread is rare and is the mechanism responsible for distant metastases. Cerebral metastasis of a cervical carcinoma was first reported in 1949 by Henriksen in an autopsy study [9]. Carcinomas of the cervix similar to other gynecologic malignancies have a low propensity to metastasize to the brain with a reported incidence of 0.4–1.2% in patients with this malignancy [10–12]. Vertebral venous system has been suggested by Chura and colleagues to be the main route of brain metastases [12].

In our two cases cervical adenocarcinoma similar to lung cancer and melanoma showed a predisposition to cause multiple intracranial metastases, whereas breast, kidney, and colorectal tumors are more likely to result in single metastatic lesions in the brain.

An estimated 80% of overall cerebral metastases occur in the cerebral hemispheres [13]. Less common sites include the cerebellum and the brainstem. This distribution is most probably

Although epidemiological studies incorporating larger population of patients is needed to support this finding, neuroendocrine differentiation in one of our cases corroborates Weed and colleagues' finding of a higher rate (33%) of cerebral metastasis in cervical neuroendocrine carcinoma in a retrospective study of 15 such cases [15]. Similar to most reported brain metastases from cervical cancer, histological evaluation of both cases here have been shown to be poorly differentiated [10, 15-19]. Our two cases as in almost all reported patients with brain metastasis from cervical cancer presented with neurologic sequelae [12]. Initial presentation of brain metastasis depends on the location of involvement, however, according to Robinson, most common initial symptoms are hemiparesis, headache, facial palsy and seizures [19]. Brain involvement in our first case presented with hemiparesis and aphasia, and in the second case severe headache was the initial symptom.

Similar to most reported patients with cervical cancer, our two cases had widely disseminated disease when brain metastases was diagnosed and especially lungs were radiographically involved as mentioned in other studies [16]. Although clinical information and histomorphology are the main sources of suspicion for accurate diagnosis, in some instances diagnosis could be quite challenging due to a wide spread involvement of multiple organs by morphologically malignant poorly differentiated glandular elements revealing focal squamous and/or neuroendocrine differentiation. In these setting using a panel of immunostains including p16 and CEA is of great value in distinguishing the primary site of the tumor.

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