

# Uterine cervical cancer with brain metastasis as the initial site of presentation

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## Abstract

Brain metastasis from uterine cervical cancer is rare, with an incidence of 0.5%, and usually occurs late in the course of the disease. We report a case of uterine cervical cancer with brain metastasis as the initial site of presentation. A 50-year-old woman with headache, vertigo, amnesia and loss of appetite was admitted for persistent vomiting. Contrast enhanced computed tomography showed a solitary right frontal cerebral lesion with ring enhancement and uterine cervical tumor. She was diagnosed with uterine cervical squamous cell carcinoma with parametrium invasion and no other distant affected organs were detected. The cerebral lesion was surgically removed and pathologically proved to be metastasis of uterine cervical squamous cell carcinoma. The patient underwent concurrent chemoradiotherapy, followed by cerebral radiation therapy, but multiple metastases to the liver and lung developed and the patient died 7 months after diagnosis of brain metastasis.

**Key words:** brain metastasis, cervical cancer, chemotherapy, craniotomy, radiotherapy.

## Introduction

Cervical cancer is the second most common cancer in women after breast cancer. Metastatic disease occurs typically by local extension and lymphatic route. Hematologic metastases, occurring less frequently, usually influence liver, lung and bone and it is estimated that 15% of cervical cancer patients develop distant metastasis during the course of the disease. Brain metastasis from uterine cervical cancer is rare, with an incidence of 0.5%.<sup>1</sup> It usually occurs late in the course of the disease, after local progression of the primary lesion or development of other distant metastases. We report a rare case of uterine cervical cancer with brain metastasis as the initial site of presentation.

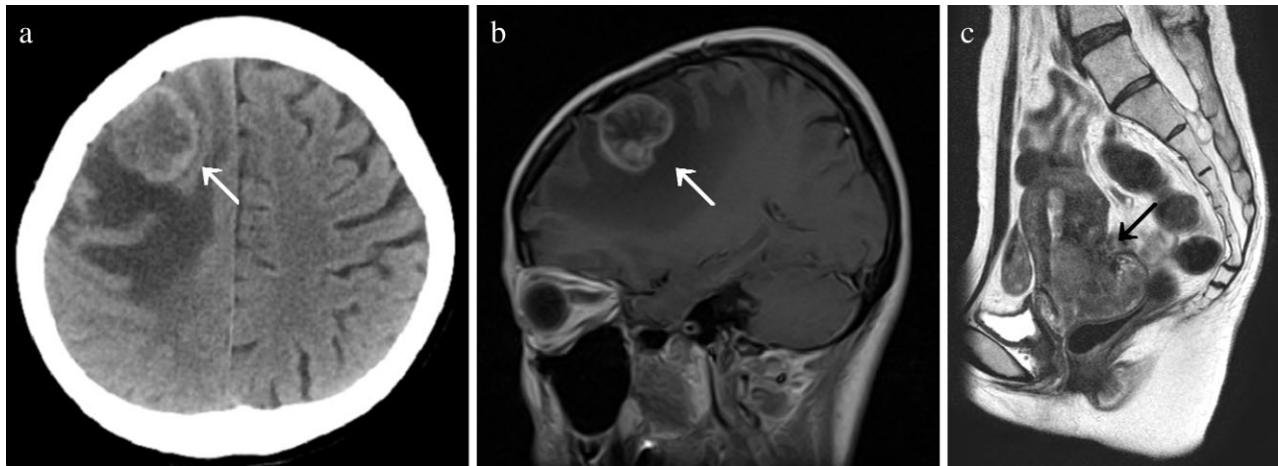
## Case Report

A 50-year-old woman (para 1-0-0-1) with no remarkable past history noted a headache and vertigo 30 days before medical visit. She also had amnesia and loss of appetite and was admitted for persistent vomiting. Physical examination indicated left hemiparesis and left facial palsy. Head contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) showed a solitary irregular-shaped right frontal cerebral lesion, measuring 30 mm, with ring enhancement and surrounding edema, compatible with metastatic brain tumor (Fig. 1). Total body contrast enhanced CT for metastatic work-up showed a 4-cm poorly enhanced tumor at the uterine cervix without any other primary lesions. The patient had never noted

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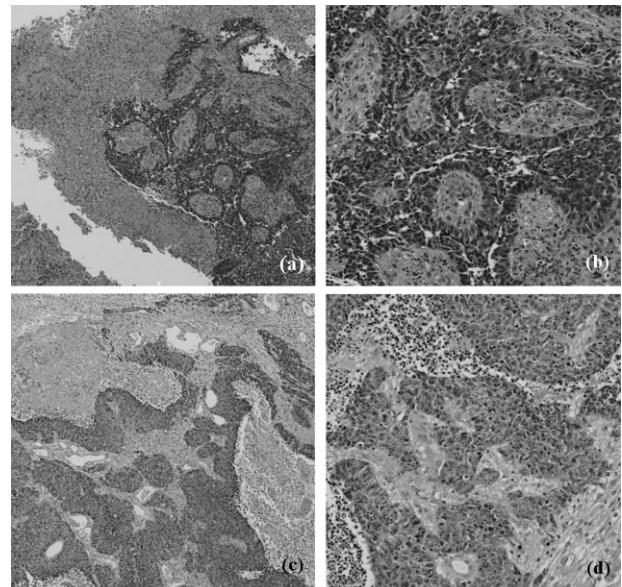


**Figure 1** (a) Contrast-enhanced computed tomography and (b) magnetic resonance imaging (MRI) showing a solitary irregular-shaped right frontal cerebral lesion (white arrow), measuring 30 mm, with ring enhancement and surrounding edema, compatible with metastatic brain tumor. (c) A poorly enhanced 4 × 6-cm cervical tumor (black arrow) with no apparent lymph node enlargement was found on pelvic contrast-enhanced MRI.

atypical genital bleeding or discharge and had no history of pap smear test. Gynecological examination showed an easily bleeding cervical tumor with bilateral parametrium invasion, while the vaginal walls were intact. On cervical biopsy a sheet formation pattern of highly cellular atypical cells infiltrating the interstitium was noted, compatible with non-keratinizing type squamous cell carcinoma (Fig. 2). Laboratory tests for tumor markers were as follows: CA125, 63.1 U/mL; CA19-9, 42.1 U/mL; carcinoembryonic antigen, 32.9 ng/mL; neuron-specific enolase, 18.2 ng/mL; and squamous cell carcinoma antigen, <0.5 ng/mL. Poorly enhanced 4 × 6-cm cervical tumor with no apparent lymph node enlargement was seen on pelvic contrast-enhanced MRI (Fig. 1).

Given that the patient's neurological condition deteriorated rapidly, the patient underwent craniotomy for intracranial pressure control and the right frontal cerebral lesion was completely resected. On microscopy, the resected specimen had a solid growth pattern of the atypical cells with a high nuclear cytoplasmic ratio, which was compatible with metastasis of uterine cervical squamous cell carcinoma (Fig. 2).

After recovery from the craniotomy, the patient received two courses of chemotherapy with irinotecan (60 mg/m<sup>2</sup>) and nedaplatin (80 mg/m<sup>2</sup>), followed by concurrent chemoradiotherapy (CCRT; 50.4 Gy/27 fr of whole pelvis irradiation and 6 Gy/4 fr intracavitary brachytherapy) with cisplatin (40 mg/m<sup>2</sup>, five courses). The primary lesion completely responded macroscopically and both cytological and histological



**Figure 2** (a,b) Cervical biopsy specimen showing a sheet formation pattern of highly cellular atypical cells infiltrating interstitium, compatible with non-keratinizing type squamous cell carcinoma (HE). (c,d) The resected craniotomy specimen showed a solid growth pattern of the atypical cells with a high nuclear cytoplasmic ratio, which was compatible with metastasis of uterine cervical squamous cell carcinoma (HE).

examination of uterine cervix was negative, while the tumor markers remained elevated after therapy. During the course of CCRT, 4 months after diagnosis, a new metastatic lesion appeared in the left parietal lobe

of the brain and the patient subsequently underwent whole brain irradiation (WBRT; 24 Gy/12 fr). One month after completion of CCRT, recurrence of the primary lesion and multiple metastases in liver, lungs, and mediastinum lymph nodes were detected. Head MRI showed enlargement of the left parietal lesion and a new metastasis in the cerebellar vermis, which caused neurological symptoms such as hemiplegia and vomiting, therefore the patient underwent stereotactic radiation therapy (SRT). The patient went into palliative care and died of the cancer 7 months after diagnosis of brain metastasis.

## Discussion

Brain metastasis is the most common intracranial tumor, accounting for >50% of brain tumors. The incidence of brain metastasis is increasing due to both improved imaging techniques and better control of extracerebral diseases resulting from systemic therapy. In adults, the most common primary diseases for brain metastasis are lung (16–20%), kidney (7–10%), breast (5%), and colorectal (1–2%) cancers and melanoma (7%).<sup>2,3</sup>

Brain metastasis from uterine cervical cancer is extremely rare, with only approximately 100 cases documented in the literature and an incidence of 0.57%.<sup>1,4–7</sup> The first report of brain metastasis of uterine cervical cancer is attributed to Henriksen in 1949.<sup>8</sup> It usually occurs late in the course of the disease, after local progression of the primary lesion or development of other distant metastases. The interval between diagnosis of cervical carcinoma and brain metastasis ranged from 0.25 months to 105 months with a median of 18 months in the reported cases.<sup>1</sup> In 78/81 reported patients (96.3%), brain metastases were detected after diagnosis of cervical cancer.<sup>1</sup> In 2007 Brown *et al.* described a patient who was diagnosed with isolated single cerebral metastasis 2 weeks after diagnosis of stage IB2 cervical adenosquamous carcinoma.<sup>9</sup> Mahmoud-Ahmed *et al.* and Buchbaum *et al.* reported cases of brain metastasis detected simultaneously on diagnosis of uterine cervical cancer.<sup>5,10</sup>

In this report, we describe our experience in diagnosing and managing a case of uterine cervical cancer with brain metastasis as the initial site of presentation. The patient had never experienced the typical symptoms of uterine cervical cancer such as atypical genital bleeding before the neurological symptoms appeared. No other organs were affected at initial diagnosis, and pathological examination of the resected brain tumor

showed squamous cell carcinoma, which was identical with the uterine cervical lesion. These observations indicated that this was a rare case of uterine cervical cancer, the diagnosis of which was preceded by the symptoms of the metastatic brain tumor. A short description of a case of brain metastasis diagnosed before the primary lesion was reported, was given by Cordeiro *et al.* in 2006, but the patient dropped out of follow-up soon after the diagnosis and never received any therapy.<sup>11</sup> To our knowledge, this is the first detailed report of diagnosis and management of uterine cervical cancer with brain metastasis as the initial site of presentation.

In approximately half of the reported cases, brain metastasis was an isolated disease confined to the brain. Half of the patients had a single metastatic lesion, and brain metastasis was located in the cerebrum in >70% of the patients.<sup>1</sup> The present patient also had a solitary cerebral lesion, and no other organs (including lungs and liver) were affected.

Symptoms and signs of brain metastases from cervical cancer are not different to those of other brain tumors. The symptoms due to increased intracranial pressure such as headache and nausea appear first, followed by the focal symptoms including seizure and paralysis,<sup>2,3</sup> which occurred in the present case as well. Most of the reported cases involved more than one symptoms at initial diagnosis.

The most common histologic type of cervical cancer with brain metastases reported in the literature is squamous cell carcinoma, but the rate of development of brain metastases is reported to be high in neuroendocrine-type carcinoma.<sup>1,7</sup> Although the present case was histologically diagnosed squamous cell carcinoma, the tumor might have contained a component of adenocarcinoma or neuroendocrine-type carcinoma, considering the fact that the elevated tumor markers were not typical for squamous cell carcinoma.

The prognosis for brain metastases originating from uterine cervical cancer is poor and the survival overall after diagnosis of brain metastases ranged from 0.1 to 72 months with a median of 4 months in the literature.<sup>1</sup> The present case was similar to the previous reports although the distant metastasis was solitary and confined to the brain.

There is no standard treatment for brain metastasis from uterine cervical cancer. Generally, patients with isolated and single brain metastasis undergo resection of the brain lesion via craniotomy followed by WBRT, while those with multiple brain metastases are given WBRT alone or with chemotherapy.<sup>1,4–7</sup> Although the

reported experience of SRT in the treatment of brain metastases from uterine cervical cancer is limited, there seems to be an advantage for use of SRT in patients who cannot tolerate craniotomy and those with surgically inaccessible lesions. The present patient had craniotomy and WBRT followed by CCRT and SRT (gamma knife radiosurgery) against the brain recurrence, which did not improve the survival overall compared with the previous reports.

Nasu *et al.* reported a retrospective study of 139 cases of brain metastases from gynecologic malignancies.<sup>12</sup> Age at diagnosis of brain metastases was significantly younger in patients with brain metastases in cervical cancer (ovarian cancer, 55.8 years of age; corpus cancer, 60.9 years; cervical cancer, 50.3 years). Most of the patients in the ovarian (85.7%) and corpus cancer groups (69.3%) had advanced stage disease (stage III/IV), but only 35.7% of those in the cervical cancer group had advanced stage disease. The cervical cancer group had the shortest median survival time of 5.0 months, whereas those in the ovarian cancer and corpus cancer groups had median survival times of 12.5 and 6.2 months, respectively. The present case was consistent with the reported features of cervical cancer with brain metastases.

There have been some reported cases of uterine endometrial cancer in which symptoms of brain metastases developed before clinical symptoms related to the primary lesion became apparent,<sup>13–15</sup> but no detailed experience of uterine cervical cancer has been reported.

Although uterine cervical cancer represents only a small fraction (3–4%) of total metastatic lesions in the brain,<sup>16</sup> we encountered a case of uterine cervical cancer diagnosed after the symptoms of brain metastasis appeared, therefore metastatic work-up should cover gynecologic malignancy including uterine cervical cancer when dealing with metastatic brain tumor.

## Disclosure

The authors have no conflicts of interest, sources of financial support, corporate involvement, or patent holdings to disclose.

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