Leptomeningeal metastasis from neuroendocrine carcinoma of the cervix: illustrative case

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BACKGROUND Leptomeningeal carcinomatosis is a rare feature of metastasis that is characterized by thickening and increased contrast enhancement throughout the meninges of the central nervous system (CNS). Leptomeningeal disease (LMD) can occur as spread from primary CNS tumors or as a manifestation of metastasis to the CNS from primary tumor sites outside the CNS. Leptomeningeal disease is, however, rare in cervical cancer, in which metastasis occurs typically from local invasion.

OBSERVATIONS The authors discuss the case of CNS metastasis with LMD from the rare neuroendocrine carcinoma of the cervix (NECC). Cervical cancer infrequently metastasizes to the CNS, but NECC is an aggressive variant with greater metastatic potential. Many of these patients will have previously received pelvic radiation, limiting their candidacy for craniospinal radiation for LMD treatment due to field overlap. This illustrative case documents the first known case of NECC CNS metastasis accompanied by LMD treated with intrathecal chemotherapy.

LESSONS Reported is the first known case of NECC with CNS metastasis accompanied by LMD. The authors highlight the potentially critical role of intrathecal chemotherapy, in addition to radiotherapy, in treating leptomeningeal metastasis from cervical cancer.

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KEYWORDS neuroendocrine carcinoma of the cervix; leptomeningeal disease; brain metastasis; cervical cancer; intrathecal chemotherapy

Illustrative Case

A 42-year-old female presented to her gynecologist with several episodes of severe abdominal pain and postcoital bleeding. Pelvic ultrasound demonstrated a large mass in the region of the vaginal canal. A biopsy sample of the lesion was taken in the office and demonstrated high-grade neuroendocrine carcinoma with positive HPV staining. The patient was treated with concurrent cisplatin/etoposide and radiation (Fig. 1). Follow-up positron emission tomography (PET) scanning reported. Here we present the first reported case of high-grade NECC metastasizing to the brain with leptomeningeal spread and discuss treatment paradigms.

ABBREVIATIONS BBB = blood-brain barrier; CSF = cerebrospinal fluid; dLMD = diffuse leptomeningeal disease; EANO = European Association of Neuro-Oncology; HPV = human papilloma virus; ITC = intrathecal chemotherapy; LMD = leptomeningeal disease; MRI = magnetic resonance imaging; NECC = neuroendocrine carcinoma of the cervix; nLMD = nodular leptomeningeal disease; NSCLC = non–small-cell lung cancer; PET = positron emission tomography; SCLC = small-cell lung cancer; SRS = stereotactic radiosurgery; XRT = radiation.
6 months later showed that the cervical mass had significantly decreased in size and there was no evidence of metastatic disease.

Seven months after diagnosis, she presented to the emergency department with episodic tingling on the left side of her body and dizziness. Brain magnetic resonance imaging (MRI) showed 5 ring-enhancing masses consistent with metastasis (Fig. 2A). She underwent 2 treatments with stereotactic radiosurgery (SRS) therapy to amenable lesions. Repeat PET scanning demonstrated relapse in the pelvic and retroperitoneal lymph nodes and pembrolizumab was added to the treatment regimen. Nine months after diagnosis, surveillance MRI after SRS showed decreased right parietal mass, increased right cerebellar metastases, and no evidence of LMD at that time (Fig. 2B).

Thirteen months after diagnosis, during the course of treatment, she presented to the emergency department with refractory and worsening headaches. Neuro-imaging and cytological analysis confirmed LMD with progression of a right cerebellar mass, obstructive hydrocephalus, and new leptomeningeal enhancement (European Association of Neuro-Oncology type IC) within the brain, cervical, and lumbar spine (Fig. 2C).

She was young, otherwise healthy, and high functioning with a Karnofsky Performance Status score of 80; therefore, she elected to undergo aggressive treatment with intrathecal topotecan chemotherapy through an Ommaya reservoir concurrent with whole-brain, cervical, and lumbar spine radiation. Craniospinal radiation was also considered but not possible given her previous pelvic radiation and concern for field overlap. Eight total treatments of 0.4 mg topotecan hydrochloride were injected intrathecally, performed twice weekly with cerebrospinal fluid (CSF) sampling for cell count and cytology. Pretreatment cytology demonstrated 5% malignant cells on one sample and 3% malignant cells on the second sample. All subsequent cytology after the first dose of intrathecal chemotherapy (ITC) remained negative for malignant cells. Despite the objective cytological response, after 1 month the patient exhibited signs of neurological progression manifest as cranial nerve V and VII palsy, syndrome of inappropriate secretion of antidiuretic hormone, and altered mental status. At this time, the patient’s family elected to discontinue treatment and transition to home hospice care, where she died 4 weeks later.

### Discussion

NECC is a rare entity first described by Albores-Saavedra et al. in 1972 of unknown cellular histogenesis. NECC tumors represent less than 1% of all female genital tract malignancies and more than 80% of these are small-cell neuroendocrine carcinoma. Unlike its more common cancerous counterparts, NECC diagnosis by Papanicolaou test (Pap smear) has a very low diagnostic accuracy, which can contribute to screening failure. Furthermore, more than 80% are associated with HPV, as was the presented patient, which could be prevented by immunization.

Management of patients with NECC remains complex due to the overall rarity and lack of established treatment algorithms and prospective studies in the literature. Therefore, most NECC treatment paradigms are extrapolated from multimodal treatment guidelines for small-cell lung cancer (SCLC) that incorporate radical resection, chemotherapy, and systemic chemotherapy with cisplatin and etoposide. Since there are no reported cases to guide management of LMD in NECC, treatment here was extrapolated from protocols established for non-SCLC (NSCLC) and breast cancer. In general, LMD portends a grim prognosis and treatment options are limited in part by poor blood-brain barrier (BBB) permeability. Therefore, ITC with combinations of methotrexate, cytarabine, and thiotepa has been established in NSCLC LMD to bypass the restrictions of the BBB. In a pooled analysis of 4 prospective and 5 retrospective studies utilizing ITC for NSCLC, cytological response was seen in 55% and radiological response in 64% of patients receiving ITC alone. ITC utilizing topotecan in the treatment of patients with breast cancer with LMD has also demonstrated success, and was the basis for the regimen selected in this case. Several case reports have also described the efficacy of systemic immune checkpoint inhibitors in patients with LMD; this strategy was also utilized in our patient. Although favorable cytological response was seen with ITC, progressive neurological decline still occurred. Given the family’s wish to transition to hospice and because no posttreatment imaging was performed, it is difficult to delineate symptom progression from ITC cytotoxicity versus cancer progression in this case.

One must also consider the type of LMD when considering prevention and treatment. The European Association of Neuro-Oncology (EANO) and the European Society for Medical Oncology recently proposed new guidelines for classification of LMD to guide therapeutic decision making according to clinical, neuroimaging, and CSF findings. Under these guidelines, type I LMD is defined by positive CSF cytology, whereas type II LMD is based on clinical and/or radiographic findings without CSF confirmation. For each type, LMD is further subclassified by MRI findings as follows: linear LMD (type A), nodular LMD (type B), mixed linear/nodular (type C), or hydrocephalus without leptomeningeal enhancement (type D). Our patient would fall under EANO type IC, positive cytology with mixed linear/nodular enhancement, which is associated with improved outcomes with intrathecal or systemic pharmacotherapy.

Kirkpatrick has suggested a simpler classification, either nodular or diffuse. Nodular LMD (nLMD) is often discrete and nodular in appearance and often thought to be associated with postoperative radionecrosis. Diffuse LMD (dLMD) is more classic in appearance with diffuse leptomeningeal thickening. In a recent multi-institutional study of patients who had undergone resection and postoperative radiation,
Prabhu et al.\textsuperscript{16} reported no significant difference between the presence of neurological symptoms with nLMD vs dLMD, but there was a significant difference in overall survival in favor of nLMD compared with dLMD (8.2 vs 3.3 months; \( p < 0.001 \)). Cagney et al.\textsuperscript{17} reported no significant difference between the rate of dLMD in surgical vs nonsurgical patients, but 0 of 870 patients in the nonsurgical group demonstrated nLMD (termed “leptomeningeal seeding” by these authors). Interestingly, our patient diverges from these reports as she presented with nLMD in absence of prior resection.

Lessons
Cancer progression with LMD remains uncommon and heralds a grim prognosis in cancer treatment. In patients with evidence of prior systemic therapy response with chemoradiation and favorable performance scores, ITC can be considered and has shown favorable cytological and radiographic responses in some patients.\textsuperscript{11} We report the first case in the literature of a patient with NECC with brain metastasis and LMD. This case also presents interesting differences from prior reported literature as our patient developed nLMD without prior neurosurgical tumor resection.\textsuperscript{17} While a limited, retrospective, observational report of 1 patient, cytological response to ITC was demonstrated and sustained. This response lends support to the potentially critical role that ITC may play in treating leptomeningeal metastasis from cervical cancer, as many of these patients will have previously received pelvic radiation, limiting their candidacy for craniospinal radiation due to field overlap. In these cases, whole-brain radiotherapy plus focal XRT of nodular components can be utilized with concurrent ITC for coverage of subclinical disease.

References


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