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SNI: Neuro-oncology

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Case Report

Small-cell neuroendocrine carcinoma of the cervix with leptomeningeal spread: A rare coincidence report and literature review

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Received: 05 June 2024
Accepted: 06 August 2024
Published: 30 August 2024

DOI
10.25259/SNI_431_2024

Quick Response Code:

ABSTRACT

Background: Metastasis from cancers of the cervix to the central nervous system is relatively uncommon. Small-cell neuroendocrine cancer of the cervix is a very rare tumor with a high tendency to spread early.

Case Description: A 33-year-old-woman was diagnosed with a small-cell neuroendocrine cancer of the cervix after complaining about a long time of post-coital bleeding. The patient was treated with eight cycles of chemotherapy and whole pelvis consolidation radiotherapy. One year later, the patient experienced local recurrence with metastases to the liver, left adrenal, and brain. Brain metastases were treated with radiosurgery. The patient started immunotherapy. Two months later, the patient was presented to the emergency department with urinary incontinence, neck pain, and difficulty walking. She was then diagnosed with craniospinal leptomeningeal disease (LMD). The patient received craniospinal palliative radiation therapy. The disease activity was severely progressive, and the patient passed out within 10 days after being diagnosed with cranial LMD.

Conclusion: A high index of suspicion for LMD is essential in patients diagnosed with cervix cancer who present with unexplained neurologic symptoms, especially with the high-grade neuroendocrine cancer type. Implementing robust research to uncover the biology of these aggressive tumors is important due to the rarity of this pathology.

Keywords: Cervix, Leptomeningeal disease, Metastasis, Neuroendocrine cell cancer

INTRODUCTION

Leptomeningeal disease (LMD) is characterized by diffuse multifocal involvement of the meninges by cancerous cells. It is considered a lethal complication of malignancy. Cancers that are associated with a high incidence of LMD include melanoma, lymphoma, leukemia, and lung and breast cancer.[1,2,4,19] Recently, the prolonged survival of patients diagnosed with cancer resulted in an increased incidence of LMD.[18,24]

Recently, cervical cancer incidence has declined due to the widespread Human papilloma virus (HPV) vaccinations and the regular screening.[6] Neuroendocrine tumors arise from

the embryonic neuroectodermal origin and frequently occur in the gastrointestinal tract, pancreas, and lung.[13] Neuroendocrine tumors of the cervix represent about 0.9–1.5% of all cervical cancers, and the small-cell variant is the most common.[28] They are associated with HPV infection and have a characteristic poor prognosis with early distant spread.[26] The limited incidence of these types of tumors makes diagnosis and treatment difficult and complicated. Brain metastases from primary cervical cancer are relatively uncommon, with an approximate estimate of 0.4–2%.[25] The incidence of LMD with primary cervical cancer is not yet reported in the literature. In this case report, we describe high-grade neuroendocrine cell cancer (NECC) metastasizing to the brain with leptomeningeal spread and discuss prognosis and the available treatment paradigms.

CASE DESCRIPTION

A 33-year-old woman was referred to a gynecological examination on June 8, 2018, due to repeated episodes of postcoital bleeding and pelvic pain. A mass lesion was detected on magnetic resonance imaging (MRI) in the cervix and upper third of the vagina and measured about 3.8 × 2.7 (AP diameter) × 3.6 (craniocaudal) [Figure 1]. Parametrium and pelvic walls were normal. Biopsy revealed an invasive high-grade neuroendocrine carcinoma, most consistent with small-cell type [Figure 2]. Immunohistochemistry revealed positive staining for synaptophysin and cytokeratin.

The patient was treated with chemotherapy in the form of eight cycles of carboplatin, etoposide, and whole pelvis consolidation radiotherapy with a dose of 4500 cGy in 25 fx, and then he received brachytherapy to the cervix and parametrium with a dose of 1400 cGy in 2 fx. One year later, the patient had a recurrence with multiple metastases affecting the liver, adrenal gland, and brain. The brain metastases were treated with Gamma Knife radiosurgery [Figure 3]. The patient then started immunotherapy in the form of ipilimumab/nivolumab.

Two months later, she presented to the emergency department with neck stiffness, cervical pain, trouble walking, and bilateral lower limb numbness associated with urinary incontinence. The patient had a Glasgow coma scale (GCS) of 15. Neurologic examination was positive only for cervical pain limitation. MRI spine revealed leptomeningeal enhancement extending from T2 superiorly through the conus medullaris and involving the cauda equina nerve roots [Figure 4]. The patient then received spine radiotherapy (20 Gy in 5 fx). One month later, she presented with lower extremity weakness, dysphagia, dysarthria, and ptosis. By this time, the patient had a GCS of 15. Neurological examination showed weak gag reflex facial nerve weakness H/B grade IV. The presentation was concerning for progressive LMD likely

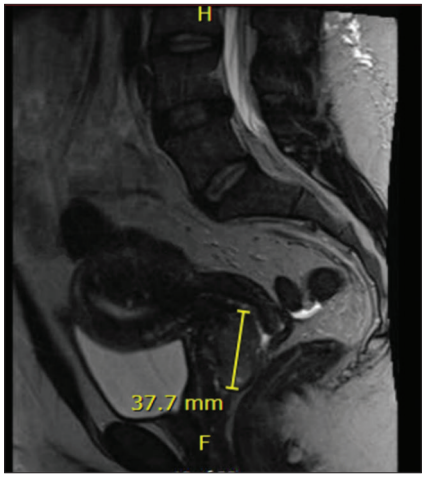

Figure 1: T2 magnetic resonance imaging with contrast of the pelvis showing a lesion in the cervix 3.8 × 2.7 (AP diameter) × 3.6 (craniocaudal). Yellow bar is a measurement tool.

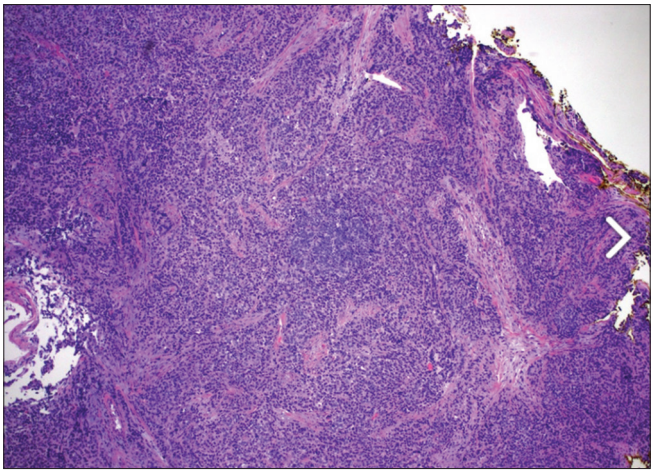

Figure 2: Hematoxylin and eosin-stained section of a biopsy from the uterine cervix showing rosette aggregates of uniform small cells with indistinct cell borders, hyperchromatic nuclei with granular chromatin.

affecting the brainstem and cranial nerves. The patient then received palliative whole brain radiation therapy (WBRT) in the form of 20 Gy/5 fractions. One week later, the patient was admitted with altered mental status. The patient was then transferred to a hospice and passed out due to aspiration and possible respiratory failure after 10 days.

DISCUSSION

Neuroendocrine cells have been identified throughout the female genital tract, frequently affecting the uterus and ovaries. In 1972, Albores-Saavedra *et al*. first identified this pathology.[2,7] The mean overall survival of neuroendocrine

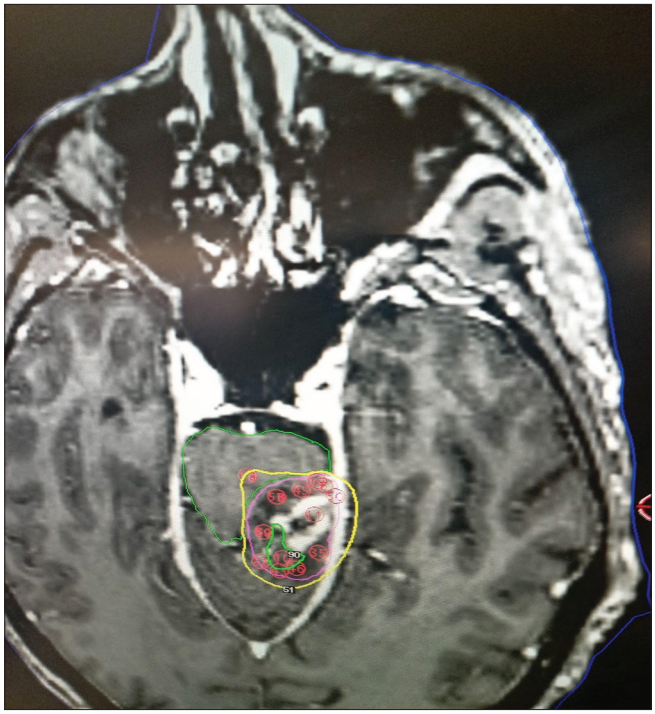

Figure 3: A posterior fossa metastatic lesion abutting the brainstem and treated with radiosurgery. The yellow line is the isodose line, the red circles are the individual treatment shots, the green line is the 90% hot spot.

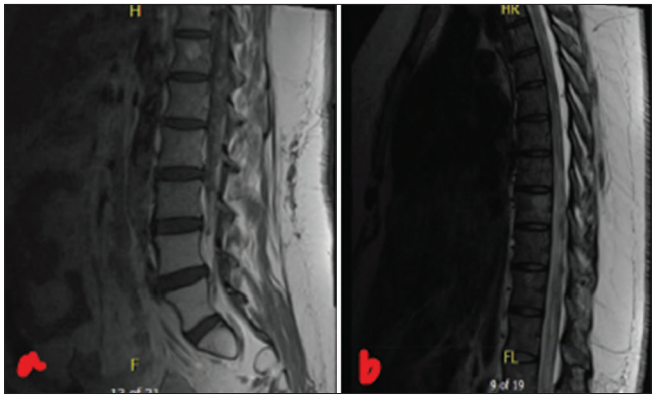

Figure 4: (a) Lumbar spine magnetic resonance imaging (MRI) T2 showing leptomeningeal enhancement along the conus and innumerable tiny nodular enhancing foci along the descending cauda equina nerve roots. (b) Thoracic spine MRI T2 with contrast showing diffuse leptomeningeal enhancement of the thoracic cord.

cervical cancer is about 40 months, with a high rate of local and distant relapses.[27] The growth pattern and the high location of the cervix make early detection of these tumors difficult.[11,18] The Pap test has a poor diagnostic value in screening for small-cell neuroendocrine cancer.[10]

The most common primary treatment reported in the literature was radical surgery combined with chemotherapy, and platinum and etoposide were the most used.[20] Despite the multidisciplinary therapeutic approaches, the overall prognosis remains poor. Pure small-cell type histology is considered an independent prognostic factor.[8]

There is only one reported case of LMD in the context of a cervical high-grade neuroendocrine tumor.[22] There are no protocols for the management of LMD in patients with cervix neuroendocrine cancer. The European Association of Neuro-oncology European Society for Medical Oncology group determined certain criteria to diagnose LMD.[16] CSF cytology or biopsy can be diagnostic. If both clinical signs and MRI features are present, LMD diagnosis is probable, while in the presence of typical MRI findings without clinical signs, LMD is possible.[15,16] Kirkpatrick further described LMD either as nodular or diffuse.[12] Prabhu *et al*. reported a significant difference in overall survival in patients diagnosed with nodular LMD compared with diffuse LMD.[23] The radiosurgical treatment of patients with brain metastases may affect the incidence of LMD. Mahajan *et al*. reported a 28% rate of LMD in surgically resected brain metastases treated with adjuvant stereotactic radiosurgery[17], while Brown *et al*. found a rate of 7% at 1 year.[5] Our patient has the features of type IC, with a typical diagnostic cerebrospinal fluid cytology and a mixed pattern of leptomeningeal enhancement.

Given the dismal prognosis of LMD, the most common treatment is palliative radiation. Clinical trials involving LMD treatment include a combination of radiotherapy, systemic therapy, and intrathecal chemotherapy; however, studies have shown variable responses to treatment, making it difficult to use a general treatment protocol.[21] The poor permeability of chemotherapies limits the systemic treatment of LMD through the blood-brain barrier. A lack of clinical trials and evidence-based treatment of cervix neuroendocrine tumors constitutes a therapeutic challenge. Due to the scarcity of similar cases, the management was the same as small-cell neuroendocrine lung cancer and included surgery, chemoradiation, and systemic chemotherapy.

Whole brain radiotherapy dismantles the integrity of the blood-brain barrier and increases the cerebrospinal fluid (CSF) concentration of systemic therapies. Circulating tumor cells in the CSF favor the use of intrathecal therapy. The most used agents for intrathecal chemotherapy are methotrexate, thiotepa, and cytarabine.[14] They can be delivered through repeated lumbar punctures or ventricular devices. Topotecan used intrathecally for the treatment of LMD in patients with breast cancer showed promising results.[9] In this case report, the patient received WBRT without any neurological improvement, and the disease was so aggressive that the patient died before starting intrathecal therapy. Table 1 summarizes similar cases of neuroendocrine cervix tumors with LMD reported in the literature.

Table 1: Similar cases of uterine cervix cancer with LMD.

Year	Age	Pathology	Time to LMD	Treatment
Kumar *et al*.,[14] 2004	39	Large cell neuroendocrine cancer	Coincident with diagnosis of primary cancer	Not mentioned
Asensio *et al*.,[3] 2009	54	Undifferentiated carcinoma with neuroendocrine differentiation	19 M	WBRT, spine palliative radiotherapy, cisplatin, and etoposide chemotherapy
Patterson *et al*.,[22] 2023	42	High-grade neuroendocrine carcinoma	13 M	Intrathecal topotecan is concurrent with whole-craniospinal radiation.
Our Case	33	High-grade small-cell neuroendocrine carcinoma	14 M	WBRT, spine palliative radiotherapy.

WBRT: Whole brain radiation therapy, LMD: Leptomeningeal disease

CONCLUSION

Clinical trials that involve small-cell neuroendocrine cell cancer (SCNECC) should be recruited to understand factors associated with LMD and determine the most efficient therapy. We report a rare case of a patient with SCNECC with brain metastasis and craniospinal LMD. The type of LMD in our case was mixed, which is different from the previously reported case.[22] Diagnosing and treating these cases is challenging, and the prognosis is disappointing.

Authors' contributions

Dr. MA contributed to designing the idea and manuscript writing, Dr. AH contributed to the final review, and Dr. HM contributed to the editing. Dr. N contributed to the table design. Dr OA contributed to the final review.

Acknowledgment

I acknowledge the equal participation of all authors in the design and production of this manuscript.

Ethical approval

The research/study was approved by the Institutional Review Board at Cairo University Hospital, number CU1335, and dated January 10, 2024.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Azab MA, Atallah O, El-Gohary N, Hazim A, Mostafa HA. Small-cell neuroendocrine carcinoma of the cervix with leptomeningeal spread: A rare coincidence report and literature review. Surg Neurol Int. 2024;15:310. doi: 10.25259/SNI_431_2024