VIA MEDICA

CASE REPORT

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Leptomeningeal metastasis in primary uterine cervical cancer: a rare case and review of the literature

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ABSTRACT

Objectives. Leptomeningeal metastasis (LM) of primary uterine cervical cancer is rare and treatment options are limited. In this case report and literature review, we aimed to present a patient with cervical cancer with LM and discuss previously reported cases in the literature.

Case presentation. Our case was a 58-year-old patient who was initially diagnosed with metastatic primary uterine cervical cancer and treated with chemotherapy and chemoradiotherapy. During follow-up, she developed neurological symptoms, and LM was detected in the craniospinal regions. Cerebrospinal fluid cytology examination has confirmed metastatic disease. The patient was treated with concurrent intrathecal methotrexate and whole-brain radiotherapy (WBRT). A good clinical and cytological response was obtained. However, while intrathecal methotrexate was being continued after WBRT, she succumbed to hematological toxicity before the radiological response could be evaluated.

Conclusions. LM is an extremely rare and catastrophic distant spread pattern in patients with cervical cancer. In the literature, a total of 26 patients were reported up to date. Median survival after detection of LM was nine weeks, including our case. Multimodal treatment combinations such as systemic and intrathecal chemotherapy and radiotherapy (RT) were used. However, most of these reports did not have detailed information about toxicity. Despite the combined use of aggressive treatment modalities, patients have limited survival and very high risks of hematologic toxicity. Concurrent use of intrathecal chemotherapy and radiotherapy should be avoided due to increased risk of morbidity.

Key words: cervical cancer, leptomeningeal metastasis, radiotherapy

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Introduction

Cervical cancer is the most common gynecological cancer worldwide and a significant health problem, particularly in underdeveloped countries [1]. At the time of diagnosis, approximately 44% of patients have localized disease, 36% have a regional disease, and 16% have distant metastasis (DM) [2]. In metastatic disease, systemic chemotherapy and palliative radiotherapy (RT) may be beneficial.

Uterine cervical cancer most commonly metastasizes to the lungs [3]. Leptomeningeal metastasis (LM) is an extremely rare site of DM in patients with uterine cervical cancer but is more common in lung cancer, breast cancer, and melanoma [4]. Leptomeningeal metastasis often causes neurological symptoms and is

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usually observed on magnetic resonance imaging (MRI). Cytological examination of the cerebrospinal fluid (CSF) sample taken by lumbar puncture is required for accurate diagnosis unless there is a contraindication. Aggressive treatment modalities, such as a combination of intrathecal chemotherapy (ITC) and RT, are often used for treatment [5]. However, the data on the management of LM in patients with uterine cervical cancer in the literature is scarce.

In this case report, we present a case of a patient with primary uterine cervical cancer who developed LM. The primary aim of this case report and literature review is to share the treatment details for this patient and discuss and compare them with previous reports.

Case presentation

A 58-year-old female was admitted in March 2020 to the Department of Pulmonology with shortness of breath and weight loss lasting two months. Her medical, family, and psycho-social history was unremarkable. The patient underwent computed tomography (CT) of the thorax and abdomen which revealed multiple mediastinal lymph nodes (LN), uterine cervical mass, bilateral parailiac LNs, and suspicious hepatic lesions. The patient was then directed to the Gynecologic Oncology Department. In the gynecological examination under general anesthesia, a necrotic and bleeding tumoral mass of 3 cm was detected in the uterine cervix, and the right parametrium was infiltrated. A pathology study of the cervical biopsy revealed a squamous cell carcinoma (SCC) of the uterine cervix. A positron emission tomography (PET)/CT was performed for staging purposes, and extensive bone and multiple liver metastases were detected in addition to the primary mass (38 × 51 mm) in the uterine cervix and left common iliac, right internal iliac, and left external iliac LNs.

The patient was then evaluated by the Gynecologic Oncology tumor board, and a decision was made to administer systemic therapy with cisplatin (50 mg/m^2, total dose: 80 mg every three weeks), paclitaxel (180 mg/m^2, total dose: 288 mg), and bevacizumab (15 mg/kg, total dose: 870 mg). Following 6 cycles, a very good metabolic response, both in the primary and metastatic sites, was observed on the PET/CT, and definitive chemoradiotherapy was planned for the primary site and regional lymphatics after reassessment by the tumor board. A 50.4 Gy volumetric-modulated arc therapy to the uterus, cervix, proximal 1/3 of the vagina, parametrial and paravaginal sites, and bilateral common, internal and external iliac, obturator and presacral lymphatics in a 1.8-Gy fraction dose with concurrent cisplatin of 40 mg/m^2/week (total dose: 60 mg) was planned and started in August 2020. However, on the MRI for brachytherapy preparation during external beam radiotherapy (EBRT), the liver metastases progressed even though the primary cervical mass and the LNs regressed, and the EBRT was stopped at 45 Gy after consideration by the tumor board. The board decided to use additional chemotherapy after completion of intracavitary brachytherapy. A total dose of 28 Gy brachytherapy was administered in 4 fractions. Following this, the patient started to receive the same chemotherapy regimen again in September 2020.

After the third cycle, the PET/CT in December 2020 revealed a complete metabolical response. Chemotherapy was stopped but bevacizumab was continued at the same dose. However, 3 months after the chemotherapy was stopped in March 2021, liver metastases progressed on the abdominal CT and weekly carboplatin (180 mg) and paclitaxel (125 mg) was initiated while bevacizumab was stopped. Following the 10th week of this regimen, the CT revealed a partial regression in the liver metastases. Two weeks after the last chemotherapy in July 2021, the patient reported pain in the right femur, and an X-ray revealed a sclerotic lesion in the distal femur. Because of the risk of pathological fracture, the patient underwent a bone curettage, cementation, and prophylactic fixation with a plaque, and a pathology examination revealed an atypical chondroid tumor of the bone. During the perioperative period, the patient could not receive any systemic therapy.

Approximately 1 month after the operation in August 2021, the patient started to report a diffuse headache and motor weakness in bilateral legs. The craniospinal MRI revealed a total of 5 cortical-meningeal metastases in the supra and infratentorial regions and extensive spinal LM, most prominent in the conus medullaris with diffuse thickening and nodular contrast enhancement in the cauda equine fibers (Fig. 1). Malignant epithelial cells were also detected in CSF cytology. which were reported as SCC metastasis of the uterine cervix. As an initial intervention, high-dose dexamethasone was administered. At this point, 2 different treatment approaches were considered by the radiation oncologists and medical oncologists; either a craniospinal irradiation (CSI) or cranial RT with intrathecal chemotherapy. Considering the possible severe toxicity of CSI, we decided to administer intrathecal methotrexate and cranial RT. Thereupon, 3 cycles of 15 mg intrathecal methotrexate were administered twice a week. Then, 30 Gy whole brain radiotherapy (WBRT) was applied in 10 fractions with concurrent 2 cycles of 15 mg of intrathecal methotrexate once a week between September 16 and 30, 2021.

Whole brain radiotherapy was well tolerated without any severe acute toxicity. A good clinical response was obtained afterward. The patient's headache completely disappeared, and her motor weakness decreased considerably. Intrathecal methotrexate was continued

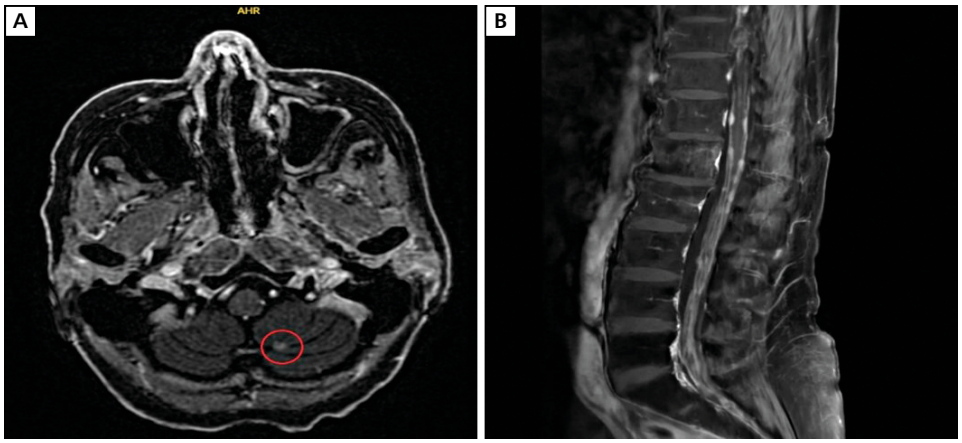

Figure 1. Cranial (**A**) and spinal (**B**) leptomeningeal metastases on magnetic resonance imaging; **A.** Cortical-meningeal metastasis in the left cerebellar region (red circle); **B.** Extensive spinal leptomeningeal metastasis in the lumbar and sacral regions

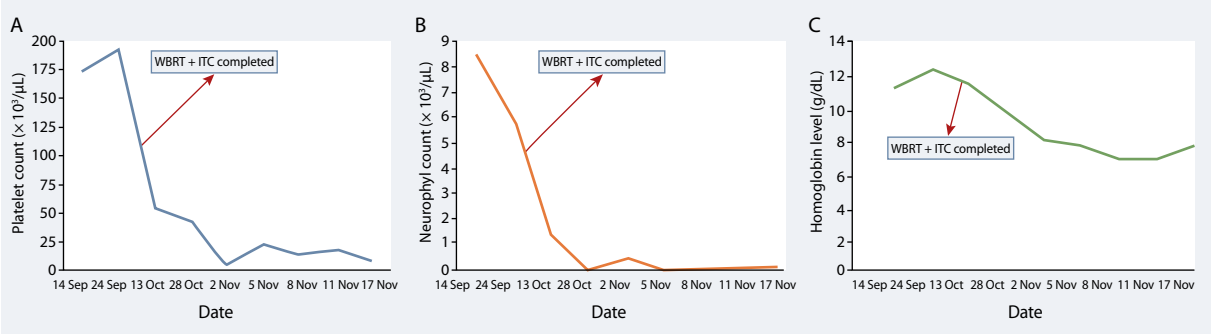

Figure 2. Hematologic parameters of the patient during treatment for leptomeningeal metastases; **A.** Platelet count/μL; **B.** Neutrophil count/μL; C. Hemoglobin levels; WBRT — whole brain radiotherapy; ITC — intrathecal chemotherapy

after WBRT for 6 weeks twice a week until CSF cytology was negative on October 28, 2021. No severe neurological toxicity was observed in the remaining life period of the patient. However, the patient developed severe thrombocytopenia and neutropenia during ITC and had to be supported by platelet suspensions and granulocyte-macrophage colony-stimulating factor. The data on the number of thrombocytes and neutrophils and the level of hemoglobin are shown in Figure 2. At the end of the third month, the patient succumbed to pancytopenia, febrile neutropenia, and septic shock due to bacterial and fungal pneumonia on November 17, 2021 before the radiological response could be evaluated.

Discussion

In patients with primary uterine cervical cancer, the incidence of DM at the time of diagnosis is approximately 16%, and the most common site is the lungs [2, 3]. Metastasis to the central nervous system is unusual. The rate of parenchymal brain metastasis of uterine cervical cancer was reported as 0.4–2.3% in the literature [6]. Leptomeningeal metastasis is even rarer, and the incidence was reported as 0.03% [7].

To the best of our knowledge, 26 cases have been reported in the literature so far, and we report the 27th patient in this case study [7–27]. We included our patient together with these 26 patients and recalculated the characteristics. Table 1 summarizes the characteristics of these 27 patients. Their median age was 47 years (range: 30–64 years), and 22% of these patients had DM at the time of diagnosis. The most common histological subtype was SCC. The latest diagnosis of LM was reported 17 years after the initial diagnosis; however, in general, LM developed within the first one to five years after initial treatment. Our patient developed LM 17 months following the initial diagnosis while under chemotherapy due to extensive metastatic disease.

Leptomeningeal metastasis of solid tumors often presents with neurologic symptoms and is usually detected by MRI. Most of the aforementioned 27 patients had neurologic symptoms consistent with lesion localization, the most common being a headache. Although

Table 1. Patient, Tumor and treatment characteristics of cervical cancer patients with leptomeningeal metastasis (LM)

Patient no.	Histology	Initial Stage	Primary treatment	Other metastasis	Time to LM diagnosis	Treatment for LM	RT field	C regimen	Survival after LM	Toxicity
#1 (7)	SCC	Localized	N/A	LNs (cervical, pelvic)	25 weeks	N/A	N/A	N/A	17 weeks	N/A
#2 (7)	SCC	Localized	N/A	Brain, buttock	190 weeks	N/A	N/A	N/A	9 weeks	N/A
#3 (7)	ASC	Localized	N/A	Lung, brain	228 weeks	N/A	N/A	N/A	46 weeks	N/A
#4 (7)	AC	Localized	N/A	Cervix, endometrium	9 weeks	N/A	N/A	N/A	14 weeks	N/A
#5 (8)	NEC	Localized	Surgery SC	Breast, lung, LNs (mediastinum, abdominal)	19 months	RT	Cranial	None	2 weeks	None
#6 (9)	SCC	Localized	Surgery RT	LNs (pelvic), Bone	836 weeks	RT	N/A	None	12 weeks	N/A
#7 (10)	SCC	Localized	RT	LNs (pelvic, PA)	39 months	SC ITC	Craniospinal	IT-MTX, S-MeCCNU	2 weeks	Facial paralysis, stomatitis, pancytopenia
#8 (11)	SCC	Metastatic	SC RT	Lung	6 weeks	Supportive care (analgesics)	None	None	2 weeks	None
#9 (12)	SCC	Localized	Surgery SC	N/A	56 weeks	RT	Cranial	None	4 weeks	N/A
#10 (13)	AC	Localized	RT	LNs (PA, SCF)	2 years	ITC RT	Cranial	IT-MTX	1 week	N/A
#11 (14)	ASC	Localized	RT	Bone	52 weeks	RT SC	Cranial	S-Cisplatin + Topotecan	8 weeks	Septic shock, DIC
#12 (15)	SCC	Localized	CRT	LNs (SCF)	2 years	ITC	None	IT-MTX	13 weeks	None
#13 (16)	ASC	Metastatic	SC	None	At diagnosis	ITC RT SC	Cranial	IT-MTX, S-carboplatin	35 weeks	N/A
#14 (17)	SCC	Localized	Surgery CRT	Brain, lung, LNs, vagina	58 weeks	RT	Cranial	None	3 weeks	N/A
#15 (18)	ASC	Localized	CRT	Liver	31 months	RT	Craniospinal	None	8 weeks	N/A
#16 (18)	NEC	Localized	CRT	Brain, bone, liver, mediastinum	19 months	RT SC	Cranial & Focal Spinal	S-Cisplatin + Etoposide	28 weeks	Infectious toxicity
#17 (19)	SCC	Metastatic	N/A	None	At diagnosis	N/A	N/A	N/A	N/A	N/A
#18 (20)	SCC	Localized	CRT	Bone, sciatic nerve	10 months	N/A	N/A	N/A	N/A	N/A
#19 (21)	SCC	Localized	CRT	LNs (PA, SCF)	34 months	ITC RT	Cranial	IT-MTX IT-Thiotepa	26 weeks	Cognitive deterioration
#20 (22)	SCC	Localized	CRT	Lung, liver, peritoneum, skin	35 weeks	RT	Cranial & Focal Spinal	None	N/A	N/A
#21 (23)	NEC	N/A	N/A	None	At diagnosis	N/A	N/A	N/A	N/A	N/A
#22 (24)	SCC	Localized	Surgery	LNs (PA, pelvic)	13 years	RT ITC	Cranial	IT-Thiotepa	9 weeks	None
#23 (25)	NEC	Metastatic	SC	Bone, LNs (pelvic, PA)	2 weeks	None	None	None	2 weeks	None
#24 (26)	AC	Localized	CRT SC	LNs (PA, pelvic)	10 months	Palliative therapy	None	None	7 weeks	None
#25 (27)	SCC	Metastatic	SC	LNs (pelvic, PA)	At diagnosis	RT SC	Cranial	S-Paclitaxel + Carboplatin	20 weeks	None
#26 (27)	SCC	Localized	Surgery RT	Lung, LNs (neck, mediastinum, axilla)	240 weeks	RT	Cranial	None	3 weeks	None
#27 (our case)	SCC	Metastatic	SC CRT	Bone, liver, LNs (pelvic, PA)	68 weeks	ITC RT	Cranial	IT-MTX	12 weeks	Pancytopenia

AC — adenocarcinoma; ASC — adenosquamous carcinoma; C — chemotherapy; CRT — chemoradiotherapy; DIC — disseminated intravascular coagulation; IT — intrathecal; ITC — intrathecal chemotherapy; LN — lymph node; MeCCNU — semustin; MTX — methotrexate; N/A — not available; NEC — neuroendocrine carcinoma; PA — paraaortic; RT — radiotherapy; SC — systemic chemotherapy; SCC — squamous cell carcinoma; SCF — supraclavicular fossa

MRI is very valuable in detecting seeding metastases, the gold standard is the cytological examination of CSF via lumbar puncture unless there is a contraindication, such as a skin infection in the puncture site, bleeding diathesis, cardio-respiratory instability, or increased intracranial pressure.

There is no effective or successful standardized treatment in patients with LM that has a poor prognosis. Intrathecal and systemic chemotherapy with various agents and WBRT with or without spinal RT were used in the cases reported so far. In general, the role of WBRT in the treatment of LM is to provide symptom palliation due to cranial involvement and improve neurological functions. Focal spinal RT may also be considered for symptom palliation in cauda equina syndrome or symptomatic gross-nodular spinal LM. Craniospinal irradiation is mostly used in the central nervous system involvement of various hematological malignancies [28]. CSI is typically not appropriate for LM of solid tumors, particularly concurrent with ITC, due to the high risk of toxicity, short life expectancy, and low likelihood of a significant benefit. On the other hand, CSI can also be applied in LM of solid tumors with acceptable toxicity rates [29]. Chemical meningitis and leukoencephalopathy are potentially serious complications of ITC administration. Concurrent use of ITC and RT raises even higher concerns because of the risk of toxicity. In a prospective study involving 59 patients with various cancers, grade 3–5 toxicity was reported in 20% of patients who received concurrent intrathecal methotrexate and RT for LM [30]. Although severe neurological toxicity has not been reported most probably due to low survival rates in patients with cervical cancer and LM, the possibility of severe toxicity due to concurrent treatment should not be underestimated.

Unlike systemic chemotherapy, the hematological toxicity of ITC is not overemphasized. However, intrathecally administered methotrexate can enter the systemic circulation via the choroid plexus and cause systemic effects such as bone marrow suppression [31]. Kose et al. [32] reported that severe hematologic toxicity may develop after intrathecal methotrexate. The majority of case reports on cervical cancer patients with LM did not mention treatment-related toxicity or the reason for death in these patients. In Weed et al. [10] study, pancytopenia was reported in a patient during intrathecal administration of methotrexate. However, the details of this toxicity were not given. In two other studies, an infectious complication was mentioned as septic shock and pneumonia, similarly without any details [14, 18]. We think that this infectious toxicity could have been related to neutropenia. Although no radiologic response could be evaluated, our patient had improved neurologic symptoms but succumbed to treatment toxicity. We believe that in other case reports without toxicity details, at least several patients could have developed severe hematologic toxicity and even succumbed to this toxicity.

Despite these aggressive treatment combinations, median survival after detection of LM was nine weeks (range: 1–46 weeks) in the 27 patients in the literature. Since patients with LM already have a limited life expectancy, every effort has to be taken in order not to impair their quality of life and cause more neurological toxicity while trying to regress the present neurologic symptoms. Although there are no high-quality data available to allow us to say that concurrent ITC and RT are safe, intrathecal methotrexate and WBRT were concurrently administered in our patient without severe neurological toxicity. It should be kept in mind that the time required for delayed neurological toxicities to occur may not have been reached due to the limited survival rate of the patient. In addition, the patient succumbed to pancytopenia and related sepsis less than 3 months after treatment. Although it is not clear whether the factor causing hematological toxicity was the combination of ITC and RT in our case, it seems highly possible.

Conclusion

There is insufficient high-quality evidence to guide the treatment of LM in patients with uterine cervical cancer. Despite the combined use of aggressive treatment modalities such as RT and ITC, the prognosis is quite poor. Improving the quality of life in this patient group with very low survival rates should be one of the most important goals, and the outcomes of treatment and toxicity should be well-balanced. In order not to cause severe hematologic toxicity, ITC with concurrent RT, even a focal WBRT should be avoided. Furthermore, de-intensifying the number of ITC to weekly doses can minimize hematologic toxicity.

Ethics statement

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patients relative for publication of the details of their medical case and any accompanying images.

Author contributions

All of the authors made significant contributions to this paper regarding the design of the manuscript, writing, and critical review in such a way that they participated sufficiently in the work to assume responsibility for the content.

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Conflict of interest

Authors declare no conflict of interest.

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