Case Report

Leptomeningeal metastases in a case of squamous cell carcinoma of the uterine cervix : A case report along with review of literature

Anupam Datta[1], Soumita Majumdar[2], Amitava Dutta[3], Partha Sen[1]

From [1]Consultant, Department of Radiation Oncology, [2]Senior Resident, Department of Radiation Oncology, [3]Consultant, Department of Pathology, Netaji Subhas Chandra Bose Cancer Hospital, Kolkata, West Bengal, India

ABSTRACT

Leptomeningeal metastases (LM) is an extremely rare complication in solid malignancies and an indicator of poor prognosis. Our case is of a 54-year-old lady who was diagnosed with squamous cell carcinoma of the uterine cervix (FIGO Stage IVA). She received 6 cycles of systemic chemotherapy with paclitaxel, carboplatin, and bevacizumab and showed near complete metabolic response in the post 6th cycle response evaluation PET CT scan. After 3 more cycles of maintenance bevacizumab, she developed disease progression. She further developed drowsiness and disorientation. Gadolinium-enhanced MRI and cerebrospinal fluid cytology confirmed the presence of LM. She was treated with craniospinal irradiation along with pembrolizumab. To date, 28 cases of LM in cervical cancer have been reported worldwide, and here we report the 29th case. There is no established treatment protocol for LM yet, and an individualized multimodality approach is commonly used based on retrospective data and patient-specific characteristics.

Key words: Carcinoma cervix, Cerebrospinal fluid cytology, Craniospinal irradiation, Leptomeningeal metastases

Leptomeningeal metastases (LM) can be defined as neoplastic involvement of the pia and arachnoid maters covering the brain and spinal cord, including the sub-arachnoid space in between. It is seen in about 1–5% of solid malignancies [1], mostly developing secondary to lung, breast, and gastrointestinal cancers or malignant melanoma. Systemic therapy that does not cross the blood–brain barrier coupled with advanced diagnostic modalities has led to improved survival in metastatic cancers. This has further led to an increase in the incidence of LM in solid malignancies.

We report a case of squamous cell carcinoma of the uterine cervix, which developed LM after achieving near complete metabolic response with chemotherapy. It is important to be aware of this manifestation since it can lead to severe neurological sequelae if not diagnosed and treated at the earliest, thereby limiting the survival of the patient. To the best of our knowledge, about 28 cases of LM in carcinoma cervix have been reported worldwide to date, and this is the 29th case.

CASE REPORT

A 54 years lady had presented with complaint of persistent, mild to moderate lower abdominal pain alongwith bleeding per vagina since a month. Whole body PET CT scan reported primary active neoplastic pathology involving cervix, upper 1/3 of vagina and lower half of uterine body, about 60 × 48 × 62 mm (SUVMax 11.8), adhering to rectal wall, infiltrating bladder wall, involving bilateral parametrium but not reaching upto lateral pelvic wall, along with extensive pelvic and para-aortic lymphadenopathy and omental deposits (Fig. 1).

Biopsy from the cervix reported poorly differentiated non-keratinizing squamous cell carcinoma. She was started on palliative chemotherapy with paclitaxel, carboplatin, and bevacizumab. Post 3 cycles response evaluation PET-CT scan reported partial response. After 6 cycles of chemotherapy, PET-CT scan showed near complete metabolic response (Fig. 2). She was started on maintenance bevacizumab. Post 3 cycles Bevacizumab, PET CT scan reported progressive disease (Fig. 3).

15 days post 3rd cycle, she presented with fever (101°F), altered sensorium, and a high blood pressure of 160/100 mmHg. A repeat punch biopsy and immunohistochemistry from the cervix reported PDL-1 positivity CPS (Combined positive score) 20%. Contrast enhanced MRI (CE-MRI) brain with screening whole spine showed leptomeningeal enhancement around the brainstem and along the cerebellar vermis and nodular leptomeningeal enhancement covering the entire spinal cord resembling a “Sugar coating” appearance (Fig. 4). Cerebrospinal fluid (CSF) cytology was positive for malignant

Access this article online	
Received - 17 March 2025 Initial Review - 04 April 2025 Accepted - 21 April 2025	Quick Response code
DOI: 10.32677/ijcr.v11i6.4962	

Correspondence to: Soumita Majumdar, Netaji Subhas Chandra Bose Cancer Hospital, 3081 Nayabad, New Garia, Kolkata - 700 094, West Bengal, India. E-mail: soumita3011@gmail.com

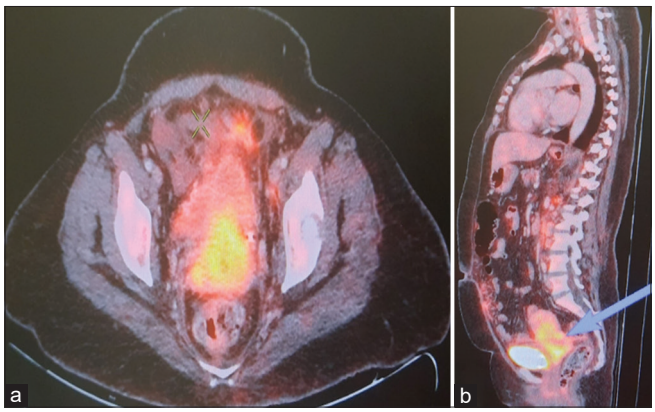

Figure 1: (a and b) Baseline PET CT scan showing active primary neoplastic pathology involving cervix, upper 1/3 of vagina and lower half of uterine body and anterior rectal wall

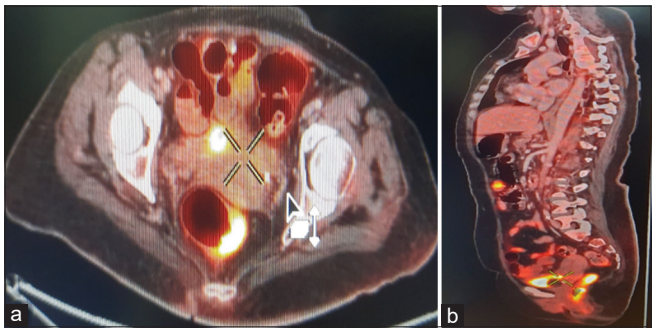

Figure 2: (a and b) Response evaluation PET CT scan post 6 cycles of chemotherapy s/o significant treatment response showing interval metabolic and morphologic regression of lower uterine body and cervix lesion

Figure 3: (a and b) PET CT scan post 3 cycles of maintenance bevacizumab showing bulky uterus with fluorodeoxyglucose avid ill-defined hypodensities involving entire uterus and cervix (SUVMax 6.4), nodular bilateral adnexa

cells (Fig. 5). The patient was planned for craniospinal irradiation (CSI) [2,3] (30.6Gy/17fractions) (Fig. 6) along with pembrolizumab [4]. After two fractions of CSI, her sensorium improved. Post 8 fractions, her general condition started deteriorating with worsening of sepsis. Radiotherapy (RT) was stopped. She expired after 3 days due to multiorgan failure.

DISCUSSION

LM is a rare but potentially life-threatening occurrence in solid tumors (3–5%) [1]. Yust-Katz *et al*. [5] reported the incidence

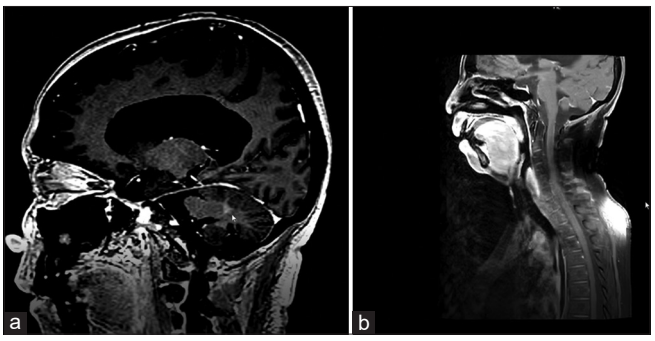

Figure 4: (a) CE-MRI brain (T1 post-contrast sagittal section image) showing subtle leptomeningeal nodular enhancement predominantly involving infratentorial compartment around the brainstem and along the cerebellar vermis; (b) MRI screening whole spine (T1 post-contrast sagittal section image) showing nodular leptomeningeal enhancement covering the entire spinal cord resembling "Sugar coating" appearance

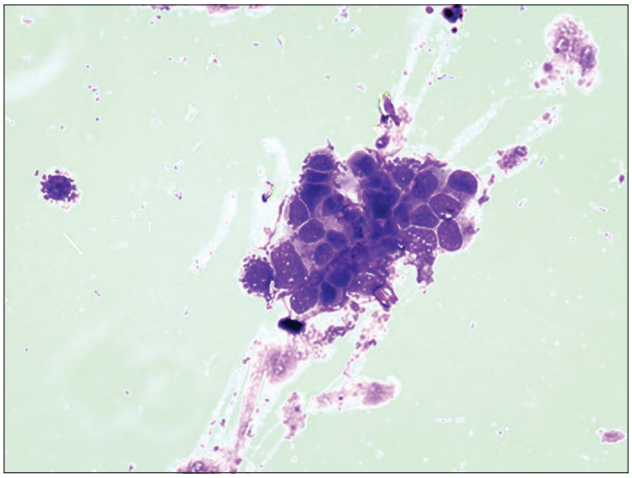

Figure 5: Photomicrograph of cerebrospinal fluid cytology (Papanicoulau stain) showing a cluster of cells with nuclear overlapping, nucleomegaly, anisonucleosis, and nuclear membrane irregularities - confirmatory of malignant cells

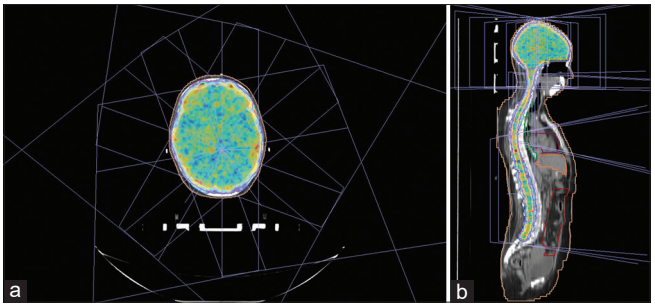

Figure 6: (a and b) Dose color wash craniospinal irradiation (IMRT). PTV covering entire brain, spinal cord including all meningeal coverings

of LM in genitourinary cancers to be 0.03% in MD Anderson Cancer Centre from 1979 to 2011. It develops due to focal or diffuse seeding of leptomeninges by malignant cells. As per the literature [5-25], the age at presentation ranged from 30 to 64 years, with a median age of 47 years. In our case, the patient's age at diagnosis is 54 years. The most common symptom of LM was headache, followed by nausea and vomiting. Our patient had

presented in a drowsy state after the development of LM. Hence, treated cases of cervical cancers presenting with neurological symptoms must be evaluated for LM.

The most common histologic type was squamous cell carcinoma, including the present case. LM usually occurs as a part of end stage disseminated disease. The probable mechanisms for the development of LM are: Hematogenous spread; direct leptomeningeal seeding from previous brain metastases, direct extension from subdural or extradural tumors and direct extension from outside of but adjacent to the CNS [7,23]. In our case, hematogenous spread seems to be the mechanism owing to the absence of metastases outside the abdominal cavity.

CSF cytology is often held as the gold standard for the diagnosis of LM. Gadolinium-enhanced MRI (Gd-MRI) helps in localizing the cause of symptoms, better visualization of the subarachnoid space and imaging of the entire neuraxis which further helps in establishing the treatment protocol for LM [26,27]. In the present case, both CSF cytology and MRI were confirmatory of the development of LM. As per the EANO - ESMO [28], a combination of clinical examination, neuroimaging, and CSF cytology is mandatory to classify and confirm the presence of LM.

Intrathecal (IT) chemotherapy has primarily been used in LM from solid malignancies, although no survival benefit has been reported to date [29]. The criteria to start IT therapy in LM are [28]: (a) No bulky LM, (b) No hydrocephalus, (c) No parenchymal brain metastases, and (d) A positive CSF cytology or presence of linear LM. Systemic chemotherapy has an insignificant role in the treatment of LM primarily due to poor penetration of blood–brain barrier and increased hematological toxicity. In our case, pembrolizumab [4] was given based on the PDL-1 positivity of the recurrent primary tumor.

Whole brain RT in the dose of 30 Gy in 10 fractions has been commonly used for palliation of symptomatic LM in ~50% of the cases, although no survival benefit with its use has been reported yet [30]. CSI is also effective in the treatment of LM with comparable survival outcomes [2]. However, the use of CSI is associated with bone marrow suppression and gastrointestinal toxicity. Advanced radiation techniques like Intensity Modulated RT (IMRT) and helical tomotherapy have shown some benefits. A randomized phase II trial showed a considerable survival benefit in patients treated with proton craniospinal RT as compared to photon-involved-field RT [3]. The median survival after diagnosis of LM ranged from 1 to 46 weeks, 5 weeks in the present case. Hence, early detection and initiation of treatment are essential to improve prognosis.

CONCLUSION

Leptomeningeal metastasis is an extremely rare complication and a very poor prognostic factor in gynecological malignancies. Only retrospective data is available on the role of radiotherapy and chemotherapy in the treatment of LM. Management should involve a multimodality approach and be focused mostly on improving the quality of life of the patient. The use of modern radiotherapy techniques such as IMRT, helical tomotherapy, and proton therapy can lead to better survival outcomes.

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Funding: Nil; Conflicts of interest: Nil.

How to cite this article: Datta A, Majumdar S, Dutta A, Sen P. Leptomeningeal metastases in a case of squamous cell carcinoma of the uterine cervix: A case report along with a review of literature. Indian J Case Reports. 2025; 11(6):273-276.