

# Leptomeningeal metastasis of poorly differentiated uterine cervical adenosquamous carcinoma following reirradiation to metastatic vertebrae

## A case report

Yueh-Feng Lu, MD<sup>a</sup>, Vai Hong Fong, MD, PhD<sup>b,c</sup>, Wen-Yih Wu, MD<sup>d</sup>, Li-Ying Wang, PhD<sup>e,f</sup>, Chen-Hsi Hsieh, MD, PhD<sup>a,g,h,\*</sup>

### Abstract

**Rationale:** Leptomeningeal metastasis from cervical adenosquamous carcinoma is extremely rare especially after radiotherapy for vertebral metastasis.

**Patient concerns:** A 52-year-old woman with International Federation of Gynecology and Obstetrics (FIGO) stage IIB adenosquamous carcinoma of cervix presented with bilateral lower limbs weakening after 2 courses radiotherapy to thoracic vertebral metastases.

**Diagnoses:** Initial spine magnetic resonance imaging (MRI) showed no obvious nerve compression, and radiation myelopathy was suspected by the clinician. Progressive multifocal neurological signs developed one month after completion of spine re-irradiation. She was diagnosed with leptomeningeal metastasis by MRI and cerebrospinal fluid (CSF) study.

**Interventions:** She received whole brain irradiation with a dose of 30 Gy in 10 fractions. Systemic chemotherapy with cisplatin (50 mg/m<sup>2</sup>) and topotecan (0.75 mg/m<sup>2</sup>) was administered sequentially.

**Outcomes:** She died with progressive disease two months after the diagnosis of leptomeningeal metastases.

**Lessons:** Poorly differentiated advanced-stage cervical adenosquamous carcinoma is an aggressive neoplasm with a worse outcome. Leptomeningeal metastasis should be included in the differential diagnosis for patients with multifocal craniospinal neurological signs. A combination of detailed neurological examinations, MRI and CSF study allowed us to establish a correct diagnosis of leptomeningeal metastasis and initiate treatment in a timely manner.

**Abbreviations:** BED = Biologically effective dose, BSCB = Blood-spinal cord barrier, CA-125 = Cancer antigen 125, CEA = Carcinoembryonic antigen, CNS = Central nervous system, CSF = Cerebrospinal fluid, FIGO = International federation of gynecology and obstetrics, ICAM = Intercellular adhesion molecules, LDH = Lactic dehydrogenase, LM = Leptomeningeal metastasis, MR-Gd = MRI with gadolinium enhancement, MRI = Magnetic resonance imaging, NF-κB = Nuclear factor kappa-light-chain-enhancer of activated B cells, PET-CT = Positron emission tomography-computed tomography, RM = Radiation myelopathy, TGF = Transforming growth factor.

**Keywords:** leptomeningeal metastasis, reirradiation, uterine cervical cancer

## 1. Introduction

Leptomeningeal metastasis (LM) results from the metastatic spread of cancer to the leptomeninges. Squamous cell and neuroendocrine carcinomas are the most common histologic

subtypes of cervical cancer associated with LM. However, LM caused by metastatic spread of cervical carcinoma is very rare, with a reported incidence of only 0.03%.<sup>[1]</sup> The symptoms and signs of LM include headache, weakness in the lower extremities, dermatomal or segmental sensory loss, cerebellar dysfunction,

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<sup>a</sup> Division of Radiation Oncology, Department of Radiology, <sup>b</sup> Department of Neurology, Far Eastern Memorial Hospital, New Taipei City, Taiwan, <sup>c</sup> Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby BC, Canada, <sup>d</sup> Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, New Taipei City, <sup>e</sup> School and Graduate Institute of Physical Therapy, College of Medicine, National Taiwan University, <sup>f</sup> Physical Therapy Center, National Taiwan University Hospital, <sup>g</sup> Department of Medicine, <sup>h</sup> Institute of Traditional Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan.

\* Correspondence: Chen-Hsi Hsieh, Division of Radiation Oncology, Department of Radiology, Far Eastern Memorial Hospital, 21 Sec 2, Nanya S Road, Banciao District, New Taipei City 220, Taiwan (e-mail: chenciab@gmail.com).

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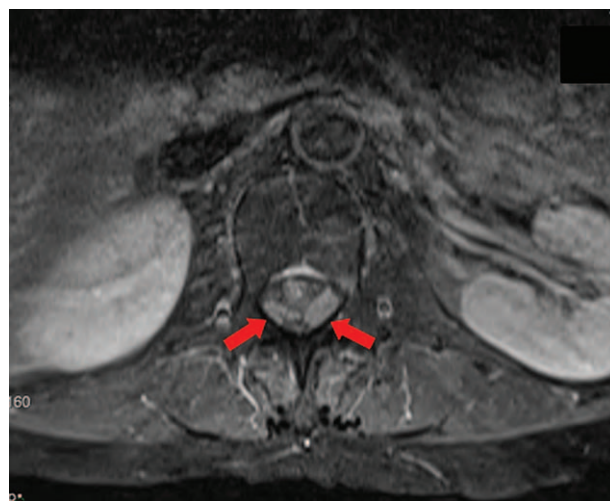


**Figure 1.** Progressive bone metastasis at the T5 vertebral body (white arrow) and numerous enhanced soft tissue lesions are seen along the cauda equina (red arrow).

altered mental status, diplopia, facial numbness, cochlear dysfunction or oculomotor neuropathy and neck or back pain.<sup>[2]</sup> Herein, we report a rare case of poorly differentiated uterine cervical adenosquamous carcinoma with leptomeningeal metastases which was misdiagnosed as radiation myelopathy after reirradiation to the 4th-5th thoracic vertebrae.

## 2. Case report

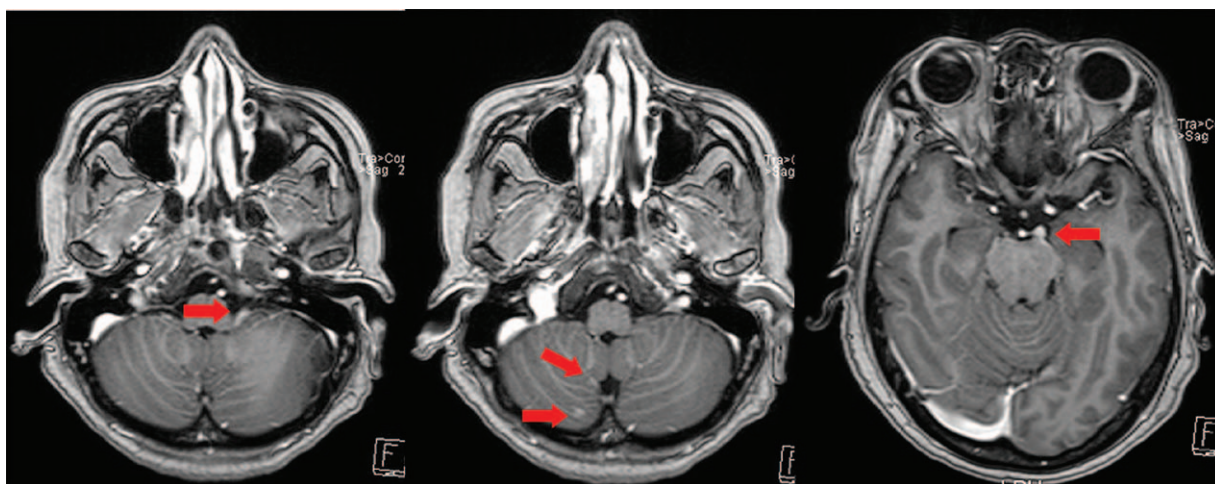
A 52-year-old woman presented with a 3-month history of abnormal vaginal bleeding in November 2013. Poorly differentiated cervical adenosquamous carcinoma stage IIB [International Federation of Gynecology and Obstetrics (FIGO)] without distant metastasis was diagnosed. The patient received whole pelvis irradiation with 50.4 Gy in 28 fractions and weekly cisplatin (40 mg/m<sup>2</sup>) followed by brachytherapy with 30 Gy in 6 fractions between November 2013 and January 2014. She remained disease-free for 3 months. In May 2014, she presented with upper back pain and bilateral leg numbness. Magnetic resonance imaging (MRI) of spine revealed a compression fracture caused by a tumor at the 4<sup>th</sup> thoracic (T) vertebra. The tumor was excised and histopathologic analysis revealed metastatic poorly differentiated carcinoma. The patient then underwent radiotherapy with 30 Gy in 10 fractions to the T3-T6 vertebral bodies.



**Figure 2.** Several enhanced lesions surround the intracanal epidural space (red arrows).

Six months later, the follow-up laboratory studies revealed elevated carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) levels and positron emission tomography-computed tomography (PET-CT) demonstrated F-fluorodeoxyglucose-avid lesions in the T4-5 vertebral bodies. The patient received radiotherapy with 25 Gy in 10 fractions to the T4-T6 vertebral bodies. Two weeks after reirradiation, she presented with bilateral lower limbs weakness. Full-spine MRI revealed radiation myelopathy at the T4-5 level without nerve compression. Prednisolone (5 mg, four times a day) was prescribed. Approximately one month later, she developed gradual onset of right-sided facial paresthesia, diplopia, hearing impairment, left-sided hemiparesis and paresis of bilateral lower limbs. She was referred to the emergency department to rule out brain metastasis; however, CT of brain did not reveal any abnormal findings.

During the following week, she experienced progressive left eyelid drooping with blurred vision and muscle weakness of lower extremities. Neurologic examination revealed left-sided ptosis, diminished direct and consensual light reflexes, as well as limited adductive, upward and downward movements of the left eye. The muscle strength of the lower extremities was fair and the patient was unable to stand up. Ankle jerk reflex was absent on the both sides. Perception of pain was diminished in the left L4 dermatome. Progressive paraplegia with hypoesthesia in the bilateral L3 to S1 territory was also noted. A lumbar puncture was performed to rule out craniospinal metastases. Analysis of the cerebrospinal fluid (CSF) revealed elevated levels of total protein (733 mg/dL; ref, 15–45 mg/dL), lactic dehydrogenase (LDH) (115 IU/L; ref, 7–40 IU/L) and CA-125 (1206 U/mL) and decreased glucose level (19 mg/dL; ref, 45–60 mg/dL). The CSF study revealed no evidence of carcinoma cells, fungus or tuberculosis infection. Follow-up MRI disclosed numerous enhanced speckled lesions at the right foramen rotundum, the left proximal oculomotor nerve, bilateral cerebellar hemispheres and along the cauda equina (Figs. 1–3). Leptomeningeal metastasis with involvement of the left oculomotor nerve, the left and right facial nerves, the left and right vestibulocochlear nerves and the cauda equina was diagnosed. The whole brain was irradiated with a dose of 30 Gy in 10 fractions. Systemic chemotherapy with cisplatin (50 mg/m<sup>2</sup>) and topotecan (0.75 mg/m<sup>2</sup>) was administered sequentially. However, her



**Figure 3.** Left panel: well-enhanced intracanalicular sheaths of the 7<sup>th</sup> and 8<sup>th</sup> cranial nerve; middle panel: several tiny enhancing nodules at the sulci of the posterior lobes in both cerebellar hemispheres; right panel: focal enlargement of the left proximal oculomotor nerve (red arrows).

condition progressively deteriorated and she died on August 10, 2015 due to septic shock with disseminated intravascular coagulation.

Retrospective data were collected after receiving approval from the Institutional Review Board of the Far Eastern Memorial Hospital (FEMH-IRB-105033-C). The need for informed consent was waived by the Institutional Review Board of the Far Eastern Memorial Hospital (FEMH-IRB-105033-C) due to the research involves no more than minimal risk to subject.

### 3. Discussion

Meningeal metastasis from malignancies of the uterine cervix is extremely rare. To the best of our knowledge, only 19 cases of this disease have been reported in the English-language literature and only 2 cases have involved adenosquamous carcinoma. Of those two, one was FIGO stage IVB<sup>[3,4]</sup> and the other was IB2.<sup>[1]</sup> After primary treatment for carcinoma of the cervix, the interval to detection of the meningeal metastases was 0 months in the patient with stage IVB disease and 57 months in the patient with stage IB2 disease. Our patient had stage IIB poorly differentiated cervical adenosquamous carcinoma and the interval to meningeal seeding was 13 months without local regional recurrence.

Advanced stage adenosquamous carcinoma is associated with a less favorable prognosis than early stage disease and other histologic subtypes.<sup>[5]</sup> Studies have shown that patients with adenosquamous carcinoma have a significantly worse survival rate (20–65%) than those with squamous cell carcinoma (83%) or patients with adenocarcinoma (80–83%).<sup>[6,7]</sup> Moreover, most patients with adenosquamous cell carcinoma die due to distant metastases.<sup>[6]</sup> Based on these findings, all grades of adenosquamous carcinoma should be considered aggressive tumors with high potential for metastasis.

Cancer cells spread to the leptomeninges via a number of routes, including direct extension from subdural or extradural tumors or from sites adjacent to the central nervous system (CNS), cell migration from systemic tumors along perineural or perivascular spaces, or hematogenous spread.<sup>[2]</sup> Repeat irradiation and high dose seems increases the risk of blood-spinal cord barrier (BSCB) dysfunction which perpetuates endothelial

permeability damage and hence increases the chances of leptomeningeal metastasis.<sup>[8]</sup> Oike et al. reported that metastasis to the leptomeninges from the uterine cervix after several times radiotherapy to different metastatic vertebral bones with relative high dose (40 Gy in 20 fractions followed by stereotactic body radiotherapy 30 Gy in 10 fractions).<sup>[3]</sup> Interestingly, LM occurred in our patient after reirradiation to vertebral bone, indicating that reirradiation to the same area or irradiation with high dose increases the risk of damage to the blood-spinal cord barrier (BSCB), which in turn increases the likelihood of cancer cells to pass through the BSCB to the meninges.

Irradiation causes oxidative stress, which enhances the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B).<sup>[9]</sup> Activation of this transcription factor stimulates the activation of inflammatory cytokines<sup>[10]</sup> and stimulates the protein expression of endothelial intercellular adhesion molecule (ICAM)-1, resulting in polymorphonuclear cell adhesion.<sup>[11]</sup> In addition, irradiation stimulates the expression of transforming growth factor (TGF)- $\beta$  and thrombin which cause extracellular matrix deposition.<sup>[12]</sup> However, the expression and activation of heparanase increases in response to irradiation.<sup>[13]</sup> These modifications of the tumor microenvironment lead to cancer metastasis.<sup>[14]</sup> Furthermore, there is a dose-dependent temporal and spatial association between radiation-induced permeability of the BSCB and apoptosis of endothelial cells.<sup>[8]</sup> Putting these published observations together, it is apparent that cancer cells can reach the meninges by direct extension from the vertebral bone through the BSCB. On the other hand, reirradiation also increases the risk of BSCB dysfunction, vasogenic edema, tissue hypoxia, which perpetuates endothelial permeability damage and hence increases the chances of leptomeningeal metastasis.<sup>[8]</sup>

The initial presentation of LM in our patient was lower limb weakness, which was initially misdiagnosed as radiation-related myelopathy because the patient received reirradiation over the thoracic spine. Clinical manifestations of radiation-induced damage in the CNS typically develop after a latent period of several months to years. Our patient received T-spine irradiation twice within an eight month period. The cumulative biologically effective dose (BED) was 131.25 Gy<sub>2</sub> and the dose

of each course was 75 Gy<sub>2</sub> and 56.25 Gy<sub>2</sub>, respectively. The risk of radiation myelopathy (RM) caused by repeated irradiation depends on the BED, the highest BED of all treatment series in a particular individual and the interval. Nieder et al. found that the risk of RM was less than 3% in patients who received a cumulative BED of  $\leq 135.5$  Gy<sub>2</sub> when the interval was not shorter than 6 months and the dose of each course was  $\leq 98$  Gy<sub>2</sub>.<sup>[15]</sup>

MRI with gadolinium enhancement (MR-Gd) has been shown to have a higher sensitivity than contrast-enhanced CT to detect patients with suspected leptomeningeal metastasis. Approximately 60–70% of cases of diffuse meningeal carcinomatosis can be detected by MR-Gd whereas CT with contrast detects abnormality in only 36% of cases.<sup>[16]</sup> In our patient, contrast-enhanced CT of brain did not detect any abnormalities and delayed the timing of treatment. The diagnosis of leptomeningeal carcinomatosis also relies on the detection of carcinoma cells in the CSF. It has been reported that approximately 30% of CSF studies in the first lumbar puncture are false negatives.<sup>[17]</sup> Nevertheless, a variety of CSF biochemical markers including alkaline phosphatase, LDH and CEA could increase the accuracy of diagnosis of LM.<sup>[2]</sup> Although CSF cytology in our patient showed mixed inflammatory cells, the fact that our patient had elevated CEA, CA-125 and LDH levels combined with clinical and MRI features characteristic of LM allowed us to establish a definitive diagnosis.

Poorly differentiated advanced-stage cervical adenosquamous carcinoma is an aggressive neoplasm with a poor prognosis. The microenvironment nearby the tumor might be changed by surgery or reirradiation to vertebral metastases, which may increase the risk of cancer cells to pass through the BSCB to the meninges. Leptomeningeal metastasis should be included in the differential diagnosis in patients with multifocal craniospinal neurological signs. A combination of detailed neurological examinations, MRI and CSF study allowed us to establish a correct diagnosis of leptomeningeal metastasis and initiate treatment in a timely manner.

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