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Case report

Spinal epidural metastasis from cervical cancer: Report of two cases and literature review

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ABSTRACT

Spinal epidural metastasis(SEM) from cervical cancer is extremely rare, with only 6 cases reported in the literature, including our reported 2 cases. SEM mostly occurs in poorly differentiated carcinoma. Hematogenous spread is the primary mechanism of SEM from cervical cancer. The patients with SEM usually present with a range of clinical manifestations of nervous system because of spinal cord compression. SEM from cervical cancer indicates a late event with a poor prognosis. Local treatments mainly include surgery decompression and radiotherapy. Combining local and systemic therapy might be a better choice to prolong survival.

1. Introduction

Spinal epidural metastasis(SEM) refers to that cancer cells metastasize to and grow in epidural space, which can result in spinal cord compression and dysfunction (Mut et al., 2005). The incidence of nervous system metastasis from cervical cancer is very low, and SEM from cervical cancer is even rarer than brain and leptomeningeal metastasis.

To our knowledge, only 6 cases of SEM from cervical cancer were reported in detail in previous literature. Here, we report the clinical features of 2 SEM cases with primary cervical cancer and review the cases reported previously.

2. Case report

2.1. Case 1

A 47-years-old woman was referred to our hospital with a diagnosis of cervical cancer and a history of massive vaginal hemorrhage. She had a 6 cm bulky tumor in the cervix with involvement of the low uterine segment and left parametrium. Pathological examination disclosed poorly differentiated squamous cell carcinoma (SCC). Computed tomography (CT) showed multiple enlarged retroperitoneal and pelvic lymph nodes, which confirmed stage IIIC2 cervical cancer (FIGO 2018). The patient underwent concurrent chemoradiotherapy in May 2017. The external-beam radiotherapy was delivered to the pelvis and paraaortic lymphatic drainage area (50.4 Gy in 28 fractions) with a simultaneous integrated boost (SIB) to the metastatic lymph nodes (60.2 Gy in 28 fractions), plus HDR(High dose rate) brachytherapy to point A (30 Gy in 5 fractions). Four courses of cisplatin were administrated simultaneously. After chemoradiotherapy, squamous cell carcinoma antigen(SCC-Ag) decreased from 8.3 ng/mL before treatment to normal.

SCC-Ag was normal until December 2020, when SCC-Ag rose to 4.8 ng/mL and she complained of right intercostal pain. Magnetic resonance imaging (MRI) revealed an epidural metastatic tumor at the level of T8-T10 with spinal cord compression and vertebral bones involvement (Fig. 1A). Positron Emission Tomography-Computed Tomography(PET-CT) revealed vertebral bone destruction of T8-10 and diaphragmatic angle metastatic lymph nodes. The patient received radiotherapy with a dose of 40 Gy in 20 fractions to bone and epidural metastases (Fig. 1B) and 50 Gy in 20 fractions to diaphragmatic angle metastatic lymph nodes. Four courses of Nimotuzumab were administrated simultaneously. After that, her intercostal pain was partially relieved and SCC-Ag decreased to 3.8 ng/mL.

Three months after radiotherapy, the patient developed multiple lymphatic and bone metastases, for which seven cycles of chemotherapy combined with targeted therapy were administered. After treatment,

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lymphatic metastases disappeared but bone metastases further developed, especially spinal cord compression by thoracic metastasis was worse. Surgical decompression was performed but the patient developed postoperative paralysis and incontinence.

2.2. Case 2

A 50-years-old woman was diagnosed with cervical cancer stage IB3 (FIGO 2018) due to vaginal bleeding after sex. A biopsy of the cervix confirmed poorly differentiated adenosquamous cell carcinoma. She underwent concurrent chemoradiotherapy from July 2015 to September 2015, consisting of pelvic radiotherapy with a dose of 50 Gy in 28 fractions, HDR brachytherapy to point A with a dose of 30 Gy in 5 fractions, and six courses of cisplatin administrated simultaneously. After initial treatment, SCC-Ag in the serum decreased from 4.9 ng/ml to 1.1 ng/ml.

Two and a half years after chemoradiotherapy, the patient underwent surgery, postoperative radiotherapy (60 Gy in 30 fractions) and four courses of chemotherapy with paclitaxel and cyclophosphamide because of lymph node metastasis in the left lung hilus. In the following two years, she developed local recurrence at the low uterine segment and vertebral bone metastasis at T7 level, during which systematic chemotherapy with cisplatin and floxuridine and radiotherapy to T7 bone metastatic area (30 Gy in 10 fractions) was given.

In January 2021, she complained of persistent needle-like pain of right arm, numbness of right leg and muscle weakness of both legs. Subsequently, SCC-Ag in the serum rose to 7.2 ng/mL and carcinoembryonic antigen(CEA) rose to 8.7 ng/mL. Cervical MRI showed abnormal enhancement of spinal dura mater and widened right intervertebral foramen at C5-7 level (Fig. 2A). Lumbar MRI showed nodular obvious enhancement within the dural sac at L3-4 level (Fig. 2A). The radiotherapy was delivered to the cervical epidural metastatic area with 30 Gy in 10 fractions with a SIB to GTV(Gross Target volume) to 35 Gy and lumbar epidural metastatic area with 30 Gy in 10 fractions with a SIB to GTV to 35–40 Gy (Fig. 2B). After radiotherapy, upper limb pain was relieved significantly and low limbs weakness was improved a little. The patient continued to receive PD-1 combined with bevacizumab within one year. After imaging evaluation, all previous metastases disappeared but iliac bone metastasis occurred on image examination.

3. Discussion

3.1. Incidence

The reported incidence of spinal epidural metastasis(SEM) in cancer patients is 5–10 %, most commonly from prostate, breast and lung cancer (Mut et al., 2005). In female genital tract cancers, spinal epidural metastasis is a rare complication. In a review of 11 comprehensive series containing 1075 cases with spinal cord compression by epidural metastasis, 27 cases(2.5 %) originated from the primary tumor of the

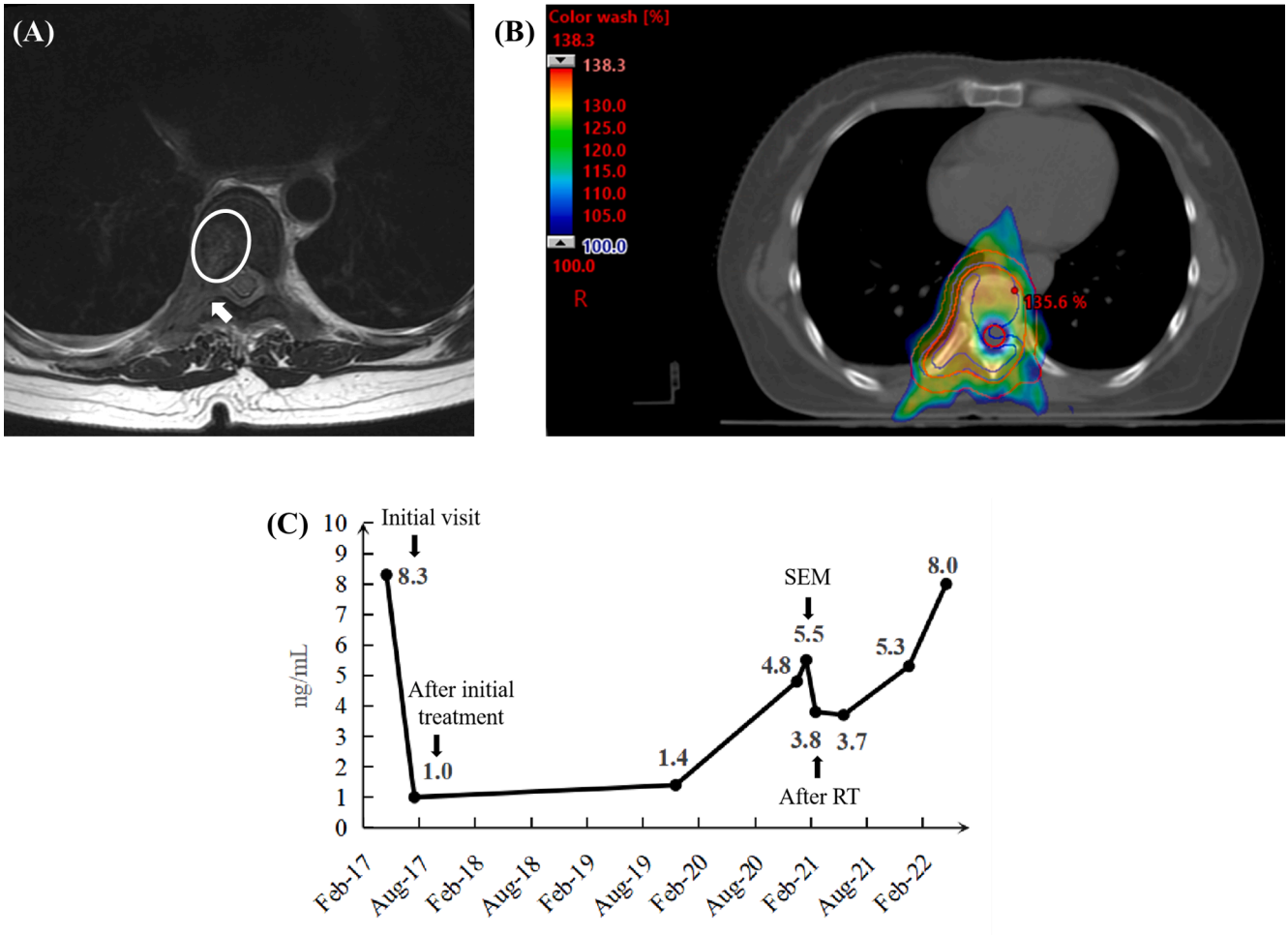

Fig. 1. Case 1. (A)MRI: Thoracic magnetic resonance imaging revealed epidural metastatic tumor with spinal cord compression and vertebral bones involvement. The circle shows vertebral bone destruction. The arrow shows metastatic tumor growing in spinal epidural space. (B)Radiotherapy dose: The clinical target volume and dose distribution image of radiotherapy to thoracic vertebral bone and spinal epidural metastasis. (C)Tumor biomarker: The trend graph of squamous cell carcinoma antigen(SCC-Ag). Abbreviation: SEM, spinal epidural metastasis ; RT, radiotherapy.

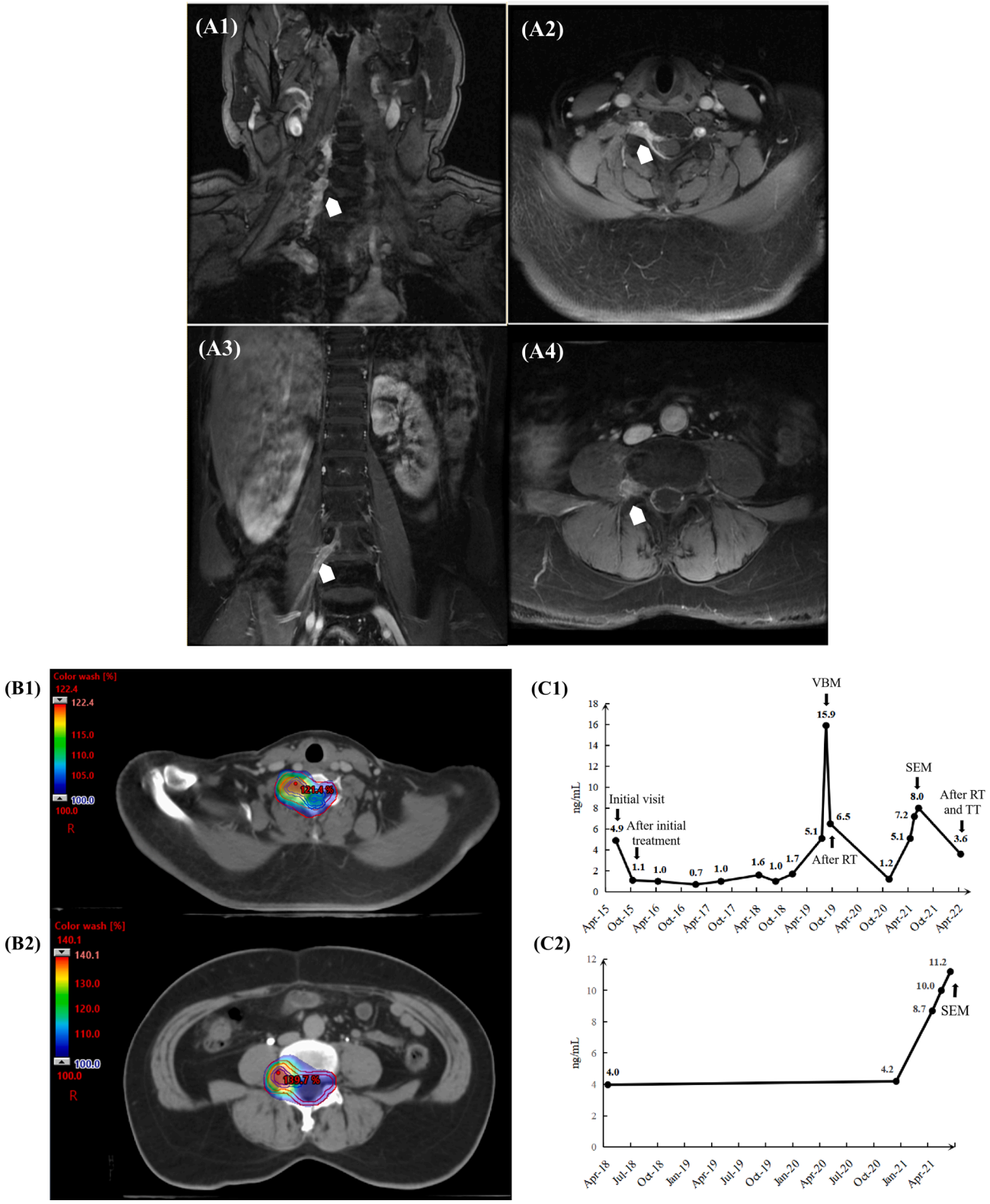

Fig. 2. Case 2. (A)MRI: Cervical magnetic resonance imaging showed abnormal enhancement of spinal dura mater and widen right intervertebral foramen at C5-7 level. Coronal image(A1) and horizontal image(A2). Lumbar magnetic resonance imaging showed nodular obvious enhancement within dural sac at L3-4 level. Coronal image(A3) and horizontal image(A4). The arrows show lesion sites of spinal epidural metastasis. (B)Radiotherapy dose: The clinical target volume and dose distribution image of radiotherapy to spinal epidural metastasis. Cervical epidural metastatic area(B1) and lumbar epidural metastatic area(B2). (C)Tumor biomarker: The trend graphs of tumor biomarkers. Squamous cell carcinoma antigen, SCC-Ag (C1) and carcino-embryonic antigen, CEA (C2). Abbreviation: VBM, vertebral bone metastasis; SEM, spinal epidural metastasis ; RT, radiotherapy; TT, target therapy.

female genital tract (Rome and Nelson, 1977). For SEM from cervical cancer, only 8 cases have been previously reported in detail (Rome and Nelson, 1977; Cormio et al., 2000; Liang and Yunmei, 2020), including our 2 cases (Table 1).

For all types of cancer, SEM is always a late event and usually occurs in the setting of widespread metastatic cancers, with a median survival time of only 3–6 months without treatment (Cole and Patchell, 2008; Taylor and Schiff, 2010). In 8 SEM cases from cervical cancer, half of the patients survived less than a year despite receiving treatment.

3.2. Mechanisms and clinical characteristics

In 8 cases of SEM from cervical cancer, the age at the initial visit was 27–55 years, with a median age of 49 years. Six cases of SEM occur in the thoracic spine, which is the most common segment for SEM because of relatively much bone bass and abundant blood flow (Mut et al., 2005; Chamberlain, 2012; Cole and Patchell, 2008). SEM from cervical cancer involves multiple histological types, including 4 cases with squamous cell carcinoma, 3 with adenocarcinoma and 1 with adenosquamous cell carcinoma. It is worth noting that the common feature of SEM from cervical cancer is poorly differentiated.

The possible mechanisms of SEM include direct extension and hematogenous spread. One of the common pathways is secondary to vertebral bone metastasis. Metastatic tumor located in the vertebral body extends posteriorly, invading the epidural space directly. Another possible pathway is the extension of paravertebral tumor through the intervertebral foramen to compress the intraspinal contents. Primary or metastatic tumors in paravertebral lymph nodes or muscles commonly produce SEM through this pathway (Mut et al., 2005; Chamberlain, 2012). Hematogenous spread transforms the cancer cell from the primary site in the pelvis to the epidural space through vascular system. Paravertebral venous plexus, also called Batson's plexus, which anastomoses with veins draining the pelvic organs, is considered to play an important role in SEM through hematogenous spread (Rades and Schiff, 2018). SEM produced through this pathway is usually limited to epidural space and without vertebral bone or paravertebral tissue involvement. Of the reported cases of SEM from cervical cancer, 7 cases didn't have metastases to vertebral bone of the corresponding segment prior to SEM and even 4 cases didn't develop any site metastasis until SEM. Therefore, the possibility of SEM through direct extension is relatively low, and hematogenous spread should be the primary mechanism of SEM from cervical cancer.

The patients with SEM can exhibit a range of clinical manifestations of the nervous system because of spinal cord or roots compression and vascular supply to spinal cord interruption (Cole and Patchell, 2008), including (1) pain, back pain is the most common, root pain in the corresponding innervated area also is present;(2) motor deficits, which varied from weakness of muscle, inability to walk, mild paresis even to complete paralysis; (3) sensory disturbance, such as numbness and hypoesthesia; (4) sphincter disturbance and incontinence. Pain, especially back pain, is considered as the earliest and most common symptom of SEM (Bates and Reuler, 1988). But in 8 SEM patients with primary cervical cancer, motor and sensory deficits are the most frequent (5/8 cases, 62.5 %). Neurologic status is a critical prognostic factor affecting health-related life quality and survival time of SEM patients after surgery (Barzilai et al., 2019). Therefore, malignant tumor patients should be evaluated in time when they complain of pain and other neurological symptoms, in order to take therapeutic measures before irreversible neurologic dysfunction develops (Taylor and Schiff, 2010).

3.3. Diagnosis

Symptoms, signs and imaging examination are the main means to diagnose SEM. Serum tumor markers play an important role in the monitoring of cervical cancer and are independent prognostic factors. Many studies have confirmed that squamous cell carcinoma antigen (SCC-Ag), cancer antigen 125 (CA125), carcino-embryonic antigen (CEA) play an important role to evaluate prognosis, therapeutic response, local recurrence and distant metastasis in cervical squamous cell carcinoma and adenocacinoma (Dasari et al., 2015; Lee et al., 2021; Zhou et al., 2017; Huang et al., 2020; Meng et al., 2021; Volkova et al., 2021; Bender et al., 2003; Kubota et al., 2019). For relatively concealed lesions, when no lesions that can explain the symptoms are found in the routine imaging examination and the serum tumor markers increase at the same time, MRI examinationis should be recommended to determine whether there is SEM. In both our 2 cases, the patients showed a significant increase in SCC-Ag and/or CEA level at the same time as the onset of neurological symptoms and these serum markers played a certain monitoring role during follow-up.

3.4. Treatment

For the local treatment of SEM, decompressive surgery followed by postoperative radiotherapy and radiotherapy alone are two conventional methods of local treatment (Cole and Patchell, 2008; Byrne, 2004). Radiotherapy has been the standard treatment of SEM for a long time and is preferred when SEM appears at multiple sites. Surgery decompression is suitable for patients with severe spinal cord compression and critical neurological dysfunction. A randomized controlled trial compared decompressive surgery followed by postoperative radiotherapy with only radiotherapy, which showed that the patients treated with surgery followed by radiotherapy had a better effect on the recovery of neurological disorders, such as restoring the ability to walk (Patchell et al., 2005).

For the systemic treatment of SEM, other metastatic lesions were found before or at the same time with SEM in 5 of the 8 cases, and 4 cases of which received systemic treatment at the same time as local treatment of SEM, the remaining one did not continue to receive systemic treatment due to poor physical condition after local treatment. 75 % of the 4 patients receiving systemic therapy had a survival of more than 1 year, which was significantly better than that of the patients without systemic therapy. In 3 of the 8 cases, patients with SEM and no other metastatic lesions only received local treatment. However, liver and lung metastasis occurred 3–6 months after local treatment of SEM. One patient only received palliative chemotherapy and the other patient refused chemotherapy. They all died within 6–12 months after the diagnosis of SEM. A study involving in 24 cases with brain metastasis indicated that the patients who underwent comprehensive treatment, such as radiotherapy and chemotherapy, had significantly prolonged survival (Sun et al., 2020). Moreover, much literature has confirmed that immunotherapy and systemic therapy have a significant effect on prolonging the life of patients with metastatic or recurrent cervical cancer (Lima et al., 2021; Mountzios et al., 2013). Therefore, considering the propensity for disseminated disease, combining multiple therapies, especially systematic treatment, might be a better choice for cervical cancer patients with SEM in good physical condition to prolong survival.

4. Conclusion

The spinal epidural metastasis of cervical cancer is extremely rare and mostly occurs in poorly differentiated carcinoma. The primary metastatic route is hematogenous spread. The patients with SEM usually present with a range of clinical manifestations of nervous system because of spinal cord compression. SEM of cervical cancer is a late event with a poor prognosis. Local treatments mainly include surgery decompression and radiotherapy. Combining local and systemic therapy might be a better choice to prolong survival.

5. Ethics and patient consent

Informed consent was obtained from each patient or her guardian

Table 1
Summary of previously reported cases of epidural metastases from cervical cancer.

Case No.	Author	Age[a]	Initial stage[b]	Histological type	Initial treatment	Recurrences prior to SEM	Clinical manifestation of SEM	Imaging examination	Location	Involvement of PVT or VB	Time to SEM[c]	Treatment for SEM	Survival after SEM
1	Rome and Nelson, 1977	50	IB	SCC	Surgery(RH)	Vagina,bladder, abdominal wall, lung, ribs and vertebral bone	Inability to walk, numbness below the waist, incontinence, back pain	X-ray	T7	Yes	3 yr 5 mo	RT, sCT(bleomycin)	1 mo
2	Rome and Nelson, 1977	53	IIIB	SCC	RT	No	Inability to walk, back pain	X-ray	L3	Yes	8 yr	Surgical decompression, RT	NK
3	Cormio et al., 2000	55	IIIC1	AC, grade III	Surgery(RH), RT	No	Radiating leg pain, complete paraplegia	X-ray	T10-L1	Yes	2 yr 1 mo	Surgical decompression, RT	6 mo
4	Cormio et al., 2000	42	IIIC1	AC, grade III	Surgery(RH), RT	Brain, lung	Leg paresis and hypoesthesia	MRI	T2-3	No	4 yr	Surgical decompression, RT, sCT(platin-based)	2 yr 1 mo
5	Cormio et al., 2000	27	IB3	AC, grade III	Surgery(RH), sCT (paclitaxel, cisplatin, epirubicin)	No	Leg hypoesthesia	MRI	T10-11	No	10 mo	Surgical decompression, RT	11 mo
6	Li and Yunmei, 2020	41	IB3	SCC, poorly differentiated	Surgery(RH), sCT (paclitaxel, cisplatin), RT	Lung, cervix	Inability to walk, numbness below the xiphoid, incontinence	MRI	T5-7	No	4 yr 6 mo	Surgical decompression	5 mo
7	Present case, 2022	47	IIIC2	SCC, poorly differentiated	CCRT	No	Intercostal pain	PET-CT, MRI	T8-10	Yes	3 yr 8 mo	RT,sCT, targeted therapy,surgical decompression	Alive at the last follow-up (1 yr 6 mo)
8	Present case, 2022	50	IB3	ASC, poorly differentiated	CCRT	Lung, cervix, vertebral bone	Arm pian, leg numbness	PET-CT, MRI	C5-7, L3-4	No	5 yr 10 mo	RT,immunotherapy	Alive at the last follow-up (1 yr 2 mo)

AC, adenocarcinoma; ASC, adenosquamous cell carcinoma; CCRT, concurrent chemoradiotherapy; LN, lymph node; mo, month(s); NK, not known; PVT, paravertebral tissue; RH, radical hysterectomy; RT, radiotherapy; SCC, squamous cell carcinoma; sCT, systemic chemotherapy; SEM, spinal epidural metastasis; VB, vertebral bones; yr, year(s).

[a] Age at diagnosis.

[b] Staging according to FIGO 2018 Staging System for Cervical Cancer.

[c] Time from initial treatment to diagnosis of epidural metastasis.

prior to initiating the treatment.

6. Author Contributions Statement

Shuai Sun put forward the conception and collected basic information and image data from the patients. Xinyue Gong organized the information on our cases and previously reported cases. The original manuscript was drafted by Shuai Sun and Xinyue Gong together, and subsequently reviewed and edited by Fuquan Zhang. All authors approved the final version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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