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Primary Intradural Extramedullary Ewing Sarcoma of the Thoracic Spine With Leptomeningeal and Brain Metastases: A Case Report and Literature Review

Achmad Harun Muchsin^{1,2}, Woochan Park³, Yu Jung Kim³, Koung Jin Suh³,
Jeong Min Seo³, Kyu Sang Lee⁴, Keun-Yong Eom⁵, Seung-Jae Hyun⁶

¹Department of Neurology, Medical Faculty of Universitas Muslim Indonesia, Makassar, South Sulawesi, Indonesia

²Division of Neuro-Oncology, Neurology Department of Medical Faculty of Hasanuddin University, Makassar, South Sulawesi, Indonesia

³Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Departments of ⁴Pathology, ⁵Radiation Oncology, and ⁶Neurosurgery, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Received September 24, 2025

Revised January 5, 2026

Accepted February 8, 2026

Correspondence

Yu Jung Kim

Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea

Tel: +82-31-787-7041

Fax: +82-31-787-4098

E-mail: cong1005@gmail.com

A 43-year-old woman presented with bilateral lower extremity weakness due to an intradural extramedullary spinal cord tumor. Surgery revealed Ewing sarcoma, a rare presentation known as primary intradural extramedullary Ewing sarcoma (PIEES). Despite initial treatment with radiation and chemotherapy, tumor recurrence occurred after 17 months. Further interventions included additional surgery, radiation, and chemotherapy. The disease progressed to leptomeningeal metastases along the spinal cord, prompting various treatments including targeted spinal radiation and systemic therapies. Brain metastases subsequently developed, necessitating whole-brain radiation and intrathecal chemotherapy. This case highlights the aggressive nature of PIEES, its potential for widespread leptomeningeal metastasis, and the challenges in its management, underscoring the need for multidisciplinary approaches in treating this rare and aggressive malignancy.

Keywords

Primary intradural extramedullary Ewing sarcoma; Ewing sarcoma; Leptomeningeal metastases.

INTRODUCTION

In 1921, James Ewing provided the initial description of Ewing's sarcoma (ES), identifying it as a malignant tumor with small, round cells that primarily affects the bone and manifests as an osteolytic lesion [1]. ES, primarily afflicting adolescents and young adults, is an exceptionally aggressive tumor that predominantly affects the bone and soft tissues and is classified within a group of neoplasms characterized by the presence of small round blue cells, including primitive neuroectodermal tumor (PNET) and Askin tumor [2]. While ES typically

originates in long bones, the pelvis, or ribs, there are rare occurrences where it emerges in extraskelatal locations, such as the paravertebral or epidural space. A primary intradural extramedullary Ewing sarcoma (PIEES) is an extremely rare subtype of extraskelatal ES [3]. PIEES is reported to progress rapidly and have a poor prognosis.

Here, we report a 43-year-old woman with bilateral lower extremity weakness who was diagnosed with an intradural extramedullary (IDEM) tumor in her spinal cord, which was later identified as ES. Despite treatments including surgery, radiation therapy, and chemotherapy, the tumor continued to spread, leading to diffuse leptomeningeal metastases (LM) and brain metastases.

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7

CASE REPORT

A 43-year-old woman was referred to our neurosurgical clinic with a one-week history of bilateral lower extremity weakness. On initial presentation, neurological examination of the lower extremities showed motor strength of Grade III on the right side and Grade IV on the left. Sensory examination revealed paresthesia in both lower extremities. Deep tendon reflexes were normal, and the patient had difficulty both urinating and defecating. At the time of initial presentation, the patient had no prior history of malignancy or other rele-

vant systemic disease. Initial sagittal T2-weighted spine MRI revealed a 6.0×1.4×1.7 cm sized IDEM mass at the right side of T11-L1 upper endplate level, with associated compressive myelopathy (Fig. 1A). Consequently, laminectomy was performed with removal of the IDEM tumor at T11-T12 (Fig. 1B). Histopathological examination of the excised tissue revealed small round cells on hematoxylin and eosin (H&E) staining. Immunohistochemical examination reconfirmed the diagnosis, with 25% of tumor cells testing positive for Ki-67, and diffuse CD99 positivity detected. EWS translocation was confirmed by fluorescence *in situ* hybridization (FISH),

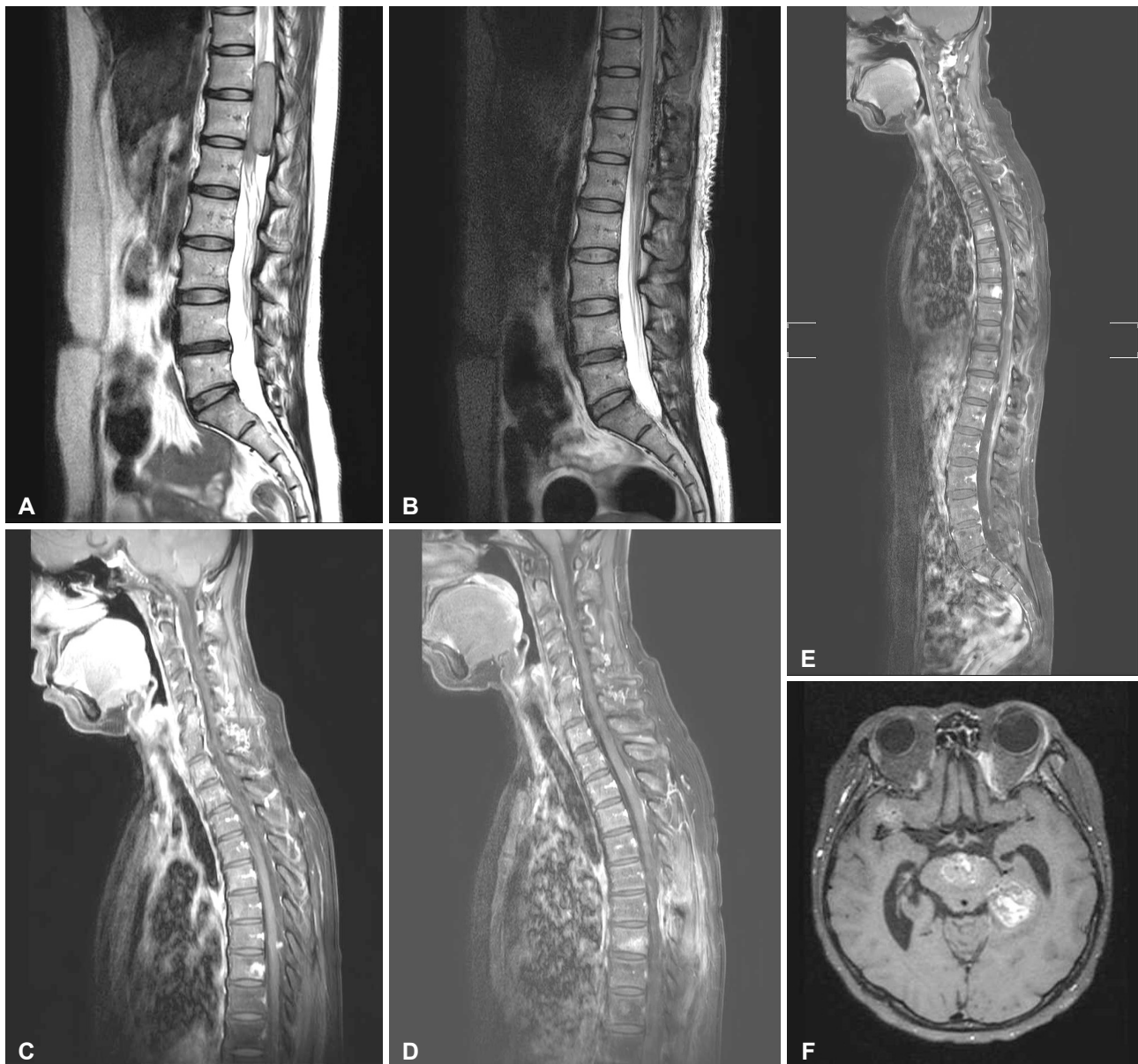


Fig. 1. Serial MRI findings. A: Preoperative T2-weighted image obtained in March 2020. B: Postoperative T2-weighted image obtained in March 2020. C: Contrast-enhanced T1-weighted image showing focal leptomeningeal metastasis in the T7 area obtained in August 2021. D: Contrast-enhanced T1-weighted image showing focal leptomeningeal metastasis in the T3 and fourth areas obtained in January 2022. E: Contrast-enhanced T1-weighted image showing diffuse leptomeningeal metastases obtained in January 2023. F: Contrast-enhanced T1-weighted image showing brain metastases obtained in July 2023.

Spinal Cord Ewing's Sarcoma With CNS Metastases

leading to the diagnosis of ES (Fig. 2). After the tumor was removed, the patient underwent postoperative radiation therapy to the thoracic spine, receiving a dose of 45 Gy in 25 fractions. Subsequently, she received eight cycles of VAC/IE chemotherapy that consists of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide, but refused further treatment after then. At 17 months after the initial surgery, and 10 months after discontinuing chemotherapy, follow-up spine MRI revealed a new 5 mm lesion in the T7 lower endplate level, consistent with focal recurrence (Fig. 1C). Interventional surgery, including laminectomy and removal of the tumor, was performed. Further treatment was postoperative radia-

tion therapy of 45 Gy in 25 fractions to the thoracic spine, and VAC/IE chemotherapy was restarted for a total of 15 cycles. A schematic sagittal illustration of the radiation fields is shown in Fig. 3.

Five months after the second surgery, subsequent MRI demonstrated a newly appeared enhancing lesion along the dorsal surface of the spinal cord, specifically at the T3 and T4 levels (Fig. 1D). Because this lesion showed a gradual increase, salvage radiation therapy to the T3-T4 area was administered at a dose of 39 Gy in 13 fractions after another 5 months.

Six months later, follow-up spine MRI showed diffuse leptomeningeal spread extending from the T5 level to the cauda

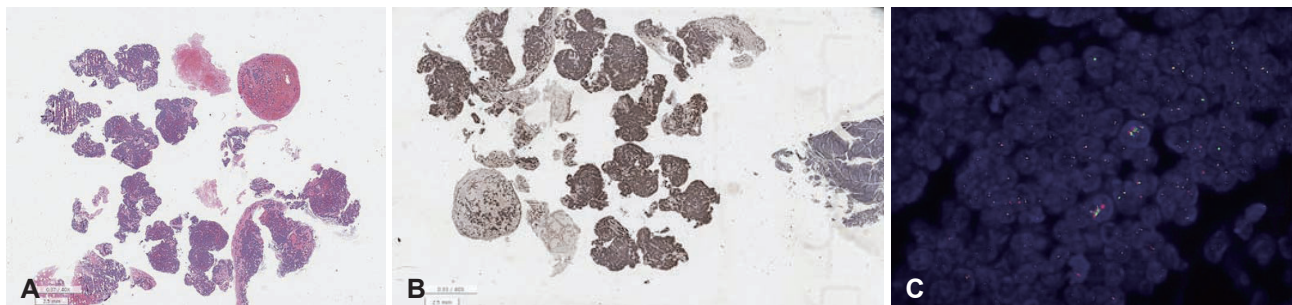


Fig. 2. Pathological examination of the excised tissue. A: Small round cells on H&E staining. B: Immunohistochemical staining demonstrating diffuse CD99 positivity. C: EWS translocation confirmed by fluorescence *in situ* hybridization (FISH).

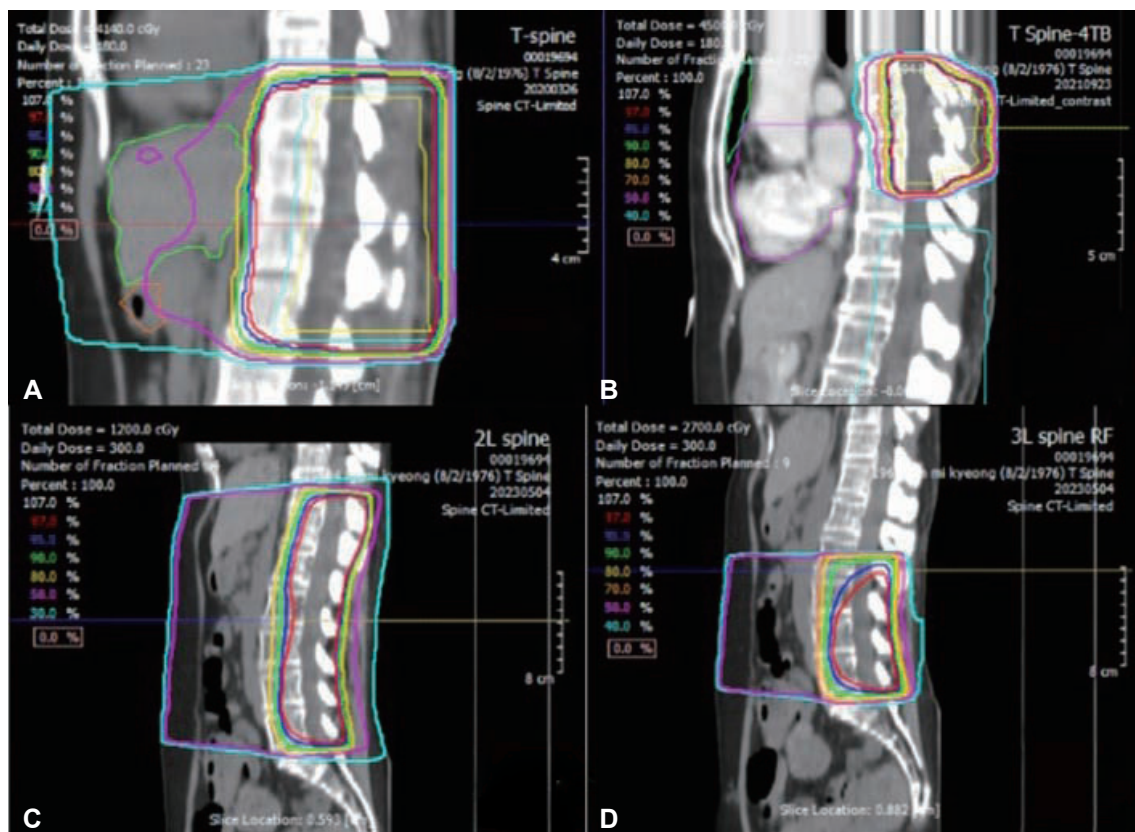


Fig. 3. Sagittal illustration of the radiation fields at different time points during the clinical course. A: Postoperative adjuvant radiation therapy (RT) delivering 45 Gy to T10–L1 (April–May 2020). B: Postoperative RT for disease progression delivering 45 Gy to T6–T9 (September–November 2021). C: Palliative RT delivering 12 Gy to T12–L5 (May 2023). D: Palliative RT delivering 27 Gy to L2–L5 (May 2023).

Table 1. Treatment timeline

Time point	Event
Month 0 (Mar 2020)	Initial diagnosis and 1st surgery
Month 1–2 (Apr 2020–May 2020)	Postoperative RT (T10–L1)
Month 2–7 (May 2020–Oct 2020)	VAC/IE chemotherapy
Month 17 (Aug 2021)	Focal recurrence (T7) and 2nd surgery
Month 18–20 (Sep 2021–Nov 2021)	Postoperative RT (T6–T9)
Month 20–34 (Nov 2021–Jan 2023)	VAC/IE chemotherapy
Month 27 (Jun 2022)	Palliative RT (T2–T5)
Month 34–37 (Jan 2023–Apr 2023)	Diffuse LM and gemcitabine/docetaxel chemotherapy
Month 38 (May 2023)	Palliative RT (C2–C7, T12–L5)
Month 38–40 (May 2023–Jul 2023)	Cabozantinib
Month 40–41 (Jul 2023–Aug 2023)	New hemorrhagic BM and palliative whole brain RT
Month 40–43 (Jul 2023–Oct 2023)	Intrathecal methotrexate, intrathecal thiotepa

RT, radiation therapy; VAC/IE chemotherapy, vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide; LM, leptomeningeal metastases, BM, brain metastases.

Table 2. Detailed description of radiation therapy

Radiation course	Site	Setting	Clinical target volume (cm ³)	Dose (Gy)	Fractionation
#1 (Mar 2020)	T10–L1	Postoperative	138.8	45	25
#2 (Sep 2021)	T6–T9	Postoperative	59.0	45	25
#3 (Jun 2022)	T2–T5	Palliative	27.2	39	13
#4 (May 2023)	C2–C7, T12–L5*	Palliative	2D	39	13
#5 (Jul 2023)	Whole brain	Palliative	2D	30	10

*12 Gy/4 fractions for T12–L1.

equina (Fig. 1E). Cerebrospinal fluid (CSF) analysis was not performed at this point and second-line treatment with gemcitabine/docetaxel was administered for four cycles, and the follow-up spine MRI showed disease progression with interval increase in LM along the whole spinal cord.

In light of the evolving disease, salvage radiation therapy was carried out on the cervical spine and lumbosacral spine at a dose of 39 Gy in 13 fractions. Concurrently, cabozantinib treatment was initiated. Unfortunately, two months later, the patient returned to the emergency room with complaints of lower extremity weakness. Subsequent MRI demonstrated further progression of LM with newly developed hemorrhagic brain metastases involving the bilateral anterior temporal lobes, left dentate gyrus, midbrain, and cerebellum (Fig. 1F). Despite widespread LM observed on MRI, CSF analysis showed no specific findings of LM and cytology was negative. Following hospitalization, intrathecal methotrexate was administered twice weekly after Ommaya reservoir insertion, while whole-brain radiation therapy was conducted at a dose of 30 Gy in 10 fractions. The patient's disease progressed despite 3 months of intrathecal chemotherapy with methotrexate and thiotepa. She was transferred to a hospice center 44 months after her initial diagnosis. The detailed treatment timeline and radiation therapy details are summarized in Tables 1 and 2.

DISCUSSION

PIEES represents an exceptionally rare manifestation of ES/PNET, with only a limited number of cases reported in the literature. While ES most commonly arises in bone or paraspinal soft tissues, intraspinal intradural development remains extremely uncommon and continues to pose substantial diagnostic and therapeutic challenges.

Clinically, affected patients most often present with axial pain and progressive neurological deficits related to spinal cord or nerve root compression, including motor weakness, sensory disturbance, and sphincter dysfunction [4]. Histopathologically, PIEES is characterized by sheets of small round blue cells, occasionally forming Homer Wright pseudorosettes [5]. Immunohistochemistry typically demonstrates strong expression of CD99 and FLI-1; however, CD99 lacks absolute specificity. Consequently, molecular confirmation—most commonly identification of the EWSR1–FLI1 fusion resulting from t(11;22)(q24;q12)—is widely regarded as a critical diagnostic feature to reliably distinguish PIEES from other intradural tumors such as meningioma or schwannoma [5,6].

Based on more than 50 cases reported in the literature, PIEES appears to predominantly affect young adults and most frequently involves the lumbosacral spine [7,8]. Gross total resection (GTR) was achieved in approximately two-

Spinal Cord Ewing's Sarcoma With CNS Metastases

12

Table 3. Summary of reported cases of recurrent primary intradural extramedullary Ewing sarcoma with leptomeningeal and/or brain metastases

Case	Study	Year	Sex/age	Location	CD99 IHC	EWS-FLI1	Surgery	Chemotherapy	Radiotherapy (Gy)	PFS* (mo)	Recurrence site	Salvage treatment	OS*	Status
1	Harimaya et al. [9]	2003	F/30	C2-C4	NR	NR	STR	Vincristine ActinomycinD Ifosfamide Doxorubicin	50	4	LM	NR	14	DOD
2	Akyüz et al. [10]	2004	F/31	L1-S1	+	NR	STR	Vincristine Lomustine Gisplatin	52.8	2	BM	Surgery	4	DOD
3	Mobley et al. [11]	2006	M/32	L2-L4	+	+	GTR	VAC/IE	55.8	8	LM	Chemotherapy	12	DOD
4	Haresh et al. [12]	2008	M/26	T11-S2	+	NR	GTR	VAC/ICE	50	2	Skip lesion (T6-T7)	Chemotherapy Radiotherapy	8	AWD after 6 months
5	Yan et al. [13]	2011	M/10	C2-C3	+	NR	GTR	None	None	1	LM	None	1	DOD
6	Bazzocchi et al. [4]	2013	F/41	L4-L5	NR	NR	GTR	VAC/IE	54	31	LM	NR	31	AWD
7	Gong et al. [14]	2015	F/39	C4-C6	+	NR	GTR	Cyclophosphamide Vincristine	38	36	Skip lesion (L4-S1)	Surgery Chemotherapy Radiotherapy	36	AWD
8	Chihak et al. [15]	2016	M/50	T11-L1	+	+	STR	VAC/IE	50.4	48	BM, LM	Surgery Radiotherapy Chemotherapy	60	DOD
9	Chihak et al. [15]	2016	M/60	L2-L3	+	+	STR	Doxorubicin Ifosfamide Etoposide	50.4	7	LM	Chemotherapy Radiotherapy	47	DOD
10	Tan et al. [16]	2019	F/34	C4-T3	+	+	STR	None	36	4	LM	Radiotherapy	11	DOD
11	Izubuchi et al. [3]	2020	F/35	T12-L1	+	+	STR	VAC/IE	45	10	BM	Chemotherapy Radiotherapy	16	DOD
12	Current study	2026	F/43	T11-T12	+	+	GTR	VAC/IE	45	17	LM, BM	Surgery Chemotherapy Radiotherapy	44	DOD

*Survival from initial diagnosis. IHC, immunohistochemistry; PFS, progression-free survival; OS, overall survival; NR, not reported; STR, subtotal tumor removal; GTR, gross tumor removal; VAC/IE, vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide; LM, leptomeningeal metastases; BM, brain metastases; DOD, dead of disease; AWD, alive with disease.

thirds of reported cases and these patients mostly received adjuvant radiotherapy and chemotherapy, but recurrence and distant metastases were frequent even after aggressive multimodal management. Selected representative cases illustrate the marked heterogeneity in clinical outcomes. For instance, durable disease control has been described following GTR in some patients, whereas others have experienced rapid progression despite subtotal resection and adjuvant radiotherapy. Notably, cases complicated by leptomeningeal dissemination and/or brain metastases, including the present patient, have generally been associated with particularly poor outcomes, suggesting an aggressive biological behavior in disseminated PIEES. We have summarized all available cases of recurrent PIEES with LM and/or brain metastases in Table 3 [3,4,8-16].

In the absence of standardized treatment guidelines, current management strategies are largely extrapolated from limited case reports and institutional experience. Multimodal treatment incorporating surgery, systemic chemotherapy, and radiation therapy has most commonly been employed. First-line chemotherapy generally follows conventional ES protocols, most frequently VAC/IE, in accordance with NCCN recommendations [17]. For relapsed or metastatic disease, second-line regimens such as cyclophosphamide/topotecan, irinotecan/temozolomide, or gemcitabine/docetaxel may be considered, while targeted agents including cabozantinib and regorafenib have demonstrated modest activity in selected patients. In the study on cabozantinib efficacy in ES called CABONE study, the objective response rate was 26% (95% confidence interval, 13–42) [18]. Unfortunately, our patient did not show response to cabozantinib.

Radiation therapy appears to play an important adjuvant role but is constrained by spinal cord tolerance [8,15]. The recommended spinal cord dose (50–55 Gy) may be suboptimal for gross residual disease, necessitating individualized treatment planning. In our case, repeated spinal radiation therapy with both adjuvant and palliative aim was performed with careful consideration of cumulative spinal cord tolerance. Although doses of approximately 50 Gy have been reported to be effective in non-metastatic PIEES, outcomes remain poor in patients with disseminated disease. Despite its limited efficacy, radiation therapy is also the main treatment modality for LM. A recent randomized phase II trial demonstrated improved central nervous system progression-free survival and overall survival with proton craniospinal irradiation compared with involved-field radiotherapy in lung and breast cancer patients with LM [19]. This approach may improve outcomes for various types of malignancies with LM in the near future.

The role of intrathecal chemotherapy in sarcoma-associat-

ed LM remains poorly defined [20,21]. Agents such as methotrexate, cytarabine, and thiopeta may provide limited benefit in selected patients but are often ineffective against solid tumor deposits and may be associated with neurotoxicity. In our patient, intrathecal therapy did not result in meaningful clinical improvement.

In summary, PIEES is a rare and aggressive entity with highly heterogeneous outcomes. Based on limited published reports, GTR combined with systemic chemotherapy and radiation therapy appears to be a commonly employed therapeutic approach; however, recurrence and metastasis remain frequent, particularly within the central nervous system. Early molecular diagnosis, careful multidisciplinary planning, and further accumulation of well-documented cases are essential to improve understanding and optimize management strategies for this challenging disease.

Ethics Statement

This study was conducted after receiving a waiver of informed consent approval from the IRB.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID iDs

Achmad Harun Muchsin	https://orcid.org/0000-0001-6271-8753
Woochan Park	https://orcid.org/0000-0002-1696-8214
Yu Jung Kim	https://orcid.org/0000-0002-5037-0523
Koung Jin Suh	https://orcid.org/0000-0002-1881-8738
Jeong Min Seo	https://orcid.org/0000-0001-9992-6273
Kyu Sang Lee	https://orcid.org/0000-0003-2801-9072
Keun-Yong Eom	https://orcid.org/0000-0003-3650-1133
Seung-Jae Hyun	https://orcid.org/0000-0003-2937-5300

Author Contributions

Conceptualization: Achmad Harun Muchsin, Yu Jung Kim. Data curation: Achmad Harun Muchsin, Woochan Park, Yu Jung Kim. Supervision: Yu Jung Kim. Writing—original draft: Achmad Harun Muchsin, Yu Jung Kim. Writing—review & editing: all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

None

Acknowledgments

None

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Spinal Cord Ewing's Sarcoma With CNS Metastases

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