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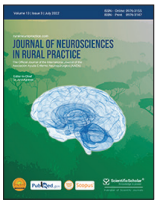

Review Article

Primary intradural extramedullary Ewing sarcoma: Review of literature and update for a standard protocol

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ABSTRACT

Ewing sarcoma (ES) is a rare, undifferentiated, and malignant mesenchymal tumor primarily affecting children and young adults. It typically presents as a lytic bone lesion located in the diaphysis of long bones or the flat bones of the pelvis, with the most common sites of metastasis being the lungs, skeletal system, and bone marrow. Primary intradural extramedullary Ewing sarcoma (IEES) is extremely rare, and its clinical presentation often overlaps with that of other spinal tumors, which can complicate diagnosis and treatment. We report a case of a young male patient, who was admitted with primary intradural extramedullary ES in the lumbar region. Magnetic resonance imaging revealed a large intradural, extramedullary mass extending from L2 to L5, with moderate contrast enhancement, initially suggesting a diagnosis of ependymoma. Consequently, the patient underwent an L2–L5 laminotomy with partial resection of the tumor. Histopathological and immunohistochemical analyses confirmed the diagnosis of IEES. After a multidisciplinary collegial evaluation of the case, the patient underwent adjuvant treatment with systemic chemotherapy. IEES is a rare condition, but it still merits consideration as a differential diagnosis of spinal tumors. Despite advances in treatment modalities, the literature review underscores the risk of local recurrence and distant metastasis, drawing attention to the importance of ideally pursuing radical surgery and effective oncologic treatment.

Keywords: Ewing sarcoma, Extra-skeletal, Intradural, Mesenchymal, Metastases, Spinal tumor

INTRODUCTION

Ewing sarcoma (ES) is a rare, undifferentiated, and malignant mesenchymal tumor originating from the neuroectoderm, primarily affecting children and adolescents. In most cases, ES manifests as a lytic bone lesion, typically located in the diaphysis of long bones or the flat bones of the pelvis. The most common sites of metastasis are the lungs, skeletal system, and bone marrow. According to the 2020 World Health Organization Classification of Soft-Tissue Tumors, ES is categorized between undifferentiated small round cell sarcoma of bone and soft tissues and presents *EWSR1* gene fusion which distinguishes it from the other subsets of the group, all differing from a clinical, pathological, and molecular point of view.[1] Extraskeletal ES subtype was first described in 1969 and usually presents as a mass in deep soft tissues with local pain involving the lower extremities, paravertebral region and chest wall, less commonly upper limb, head, neck, pelvis, and the retroperitoneal region.[2] Compared to classical ES, the distribution is bimodal, with peaks evident both below 5 years and above 35 years of age, and shows no sex predominance. Moreover, primary intradural extramedullary ES (IEES) is an extremely rare spinal cord tumor, and the resemblance of its presentation to other spinal tumors, such as schwannomas, meningiomas, and ependymomas, further complicates its identification and management. It, therefore, poses unique diagnostic and therapeutic challenges.

Here, we present the case of a young male patient with primary IESS in the lumbar region, who was admitted to Centro Traumatologico Ortopedico of Città della Salute e della Scienza (Turin, Italy) in November 2023. This case is accompanied by a review of the existing literature and the proposal of a flowchart outlining a standard protocol for the diagnosis and management of such cases.

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CASE REPORT

A 36-year-old male presented with worsening lower back pain, radiating down the lower right extremity, which had been progressively increasing over the course of one year despite poor response to pain relief therapy with non-steroidal anti-inflammatory drugs. He later developed burning paresthesia, gait difficulty due to dorsiflexion deficiency of the right foot, and a feeling of incomplete defecation and urination with persistence of urge after voiding.

Lumbar magnetic resonance imaging (MRI) revealed a large intradural extramedullary mass in the cauda equina, extending from the lower endplate of L2 to the upper endplate of L5, with a vertical length of 7.5 cm, completely filling the spinal canal [Figure 1]. The mass had a solid appearance and showed hypointensity on T1-weighted images, isointensity on T2-weighted images, and a modest, slightly inhomogeneous, contrast enhancement, suggesting the diagnosis of a probable myxopapillary ependymoma.

Neurological physical examination revealed significant sthenic deficiency in the lower right limb (Medical Research Council [MRC] 4/5 at thigh flexion and leg extension, MRC 3/5 at foot dorsiflexion, and MRC 2/5 at foot plantar flexion) with hypoelicitable patellar osteotendinous reflex associated. Signs of upper motor neuron suffering were present in the left lower limb (lively osteotendinous reflexes with reflexogenic area extension).

During hospitalization, an MRI of the whole spine was also performed, which showed no further expansive lesions at the endocanal level.

The patient was referred to the neurosurgery department and underwent an L2–L5 laminotomy. Due to the extensive involvement of nerve roots surrounding the tumor and the decreased amplitude observed in intraoperative neurological monitoring, only a partial resection of the tumor was performed. During the surgery, a reduction in the amplitude of both motor-evoked potentials and somatosensory-evoked potentials was recorded, particularly in the distal part of the right lower limb.

Pain and paresthesia in lower limbs disappeared after the surgery and the patient recovered completely from the proximal muscle weakness of the right lower limb. On the other hand, right foot dorsi- and flexion did not improve (MRC 1/5). In addition, weaning from the bladder catheter proved impossible due to persistent urinary retention.

Histological examination of hematoxylin and eosin slides showed fragments of dense connective tissue populated by a proliferation of undifferentiated small round cells with irregular nuclei, high nucleus-to-cytoplasm ratio, sparse chromatin, and either absent or clear cytoplasm [Figure 2]. Rare mitotic figures were present as well (2/10 High-Power Field).

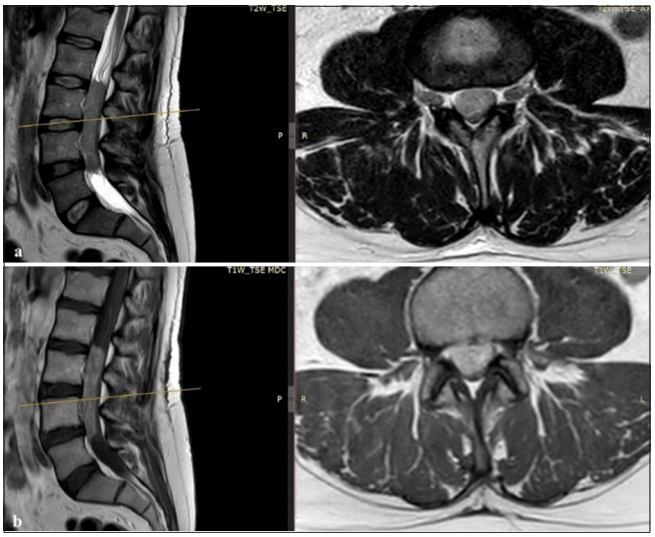

Figure 1: (a) Sagittal and axial lumbar MRI images. T2 non-contrasted sequence showing low T2 signal-intensity intradural/extramedullary lesion extending from the lower aspect of L2 to L4–L5 disc level. (b) Sagittal and axial T1 contrasted image showing diffuse homogenous enhancement of the lesion. L: Lesion, T1W: T1-weighted MRI image without contrast, T2W: T2-weighted MRI image without contrast, TSE: Turbo spin echo, MDC: Mezzo di contrasto (contrast agent), AX: Axial, P: Posterior, R: Right, L: Left.

Immunohistochemical reactions showed diffuse membrane positivity for CD99 and nuclear positivity for NKX2.2. INI1 expression was retained. Stainings for cytokeratins AE1/AE3, desmin, S100, GFAP, CD34, chromogranin A, synaptophysin, Wilms tumor Gene 1 (WT1), leukocyte common antigen (LCA), CD3, and CD20 were negative.

After diagnosis, the patient underwent a positron emission tomography (PET)-computed tomography (CT), which ruled out the dissemination of the disease. After a multidisciplinary collegial evaluation of the case, the patient underwent adjuvant treatment with systemic chemotherapy (ChT) (including doxorubicin + cyclophosphamide), and any radiotherapy (RT) was postponed until the reduction of the tumor mass with the intention of preserving the enveloped nerve roots as much as possible. At this time, the patient received three cycles of ChT without complications.

DISCUSSION

IEES is an extremely rare pathology, with very few cases reported to date. Table 1 shows a summary of them.[3-33] Lumbar region is the predominant site of lesion, followed by the cervical region. Respected to Iacoangeli *et al.*, this review articles with spinal secondarism of EW or general spinal intradural metastases were excluded, as having a homogenous summary.[31]

About 34% (n = 13) of the assessed 38 patients were female and 66% (n = 25) were male. The mean age of the cohort was

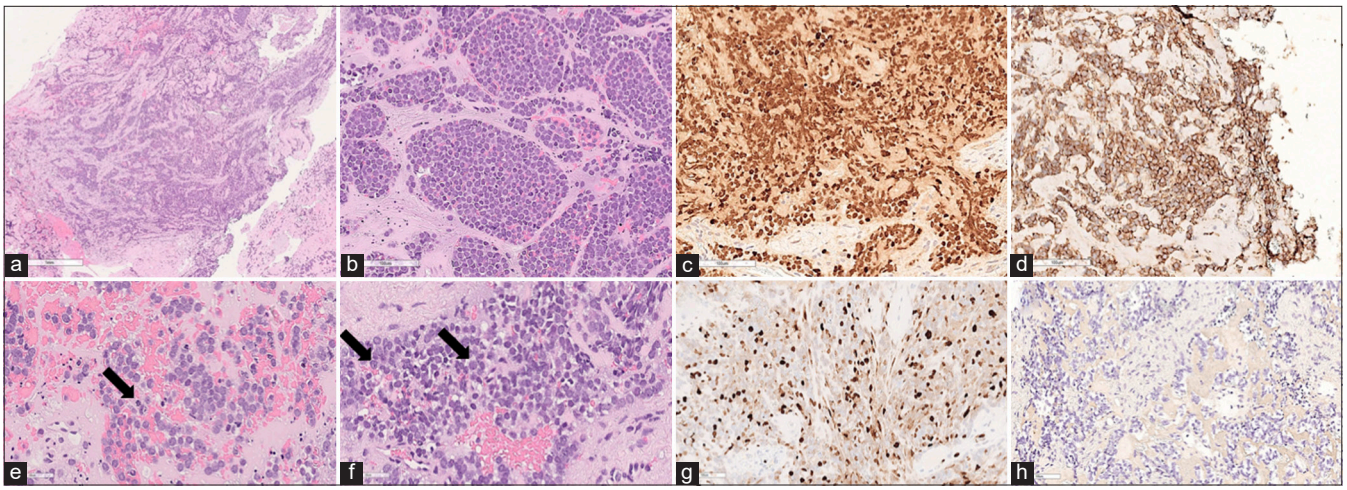

Figure 2: Photomicrographs of the resected specimen. (a-d) Hematoxylin and eosin stain shows a dense proliferation of small round cells with scant to absent cytoplasm, high nucleus/cytoplasm ratio with fine strippled chromatin, (c, arrow) sparse mitoses and (d, arrow) small nucleoli. (e) Immunohistochemical reactions demonstrating diffuse nuclear positivity for NKX2.2, (f) membranous positivity for CD99 and (g) a proliferation index of 40%. (h) Staining for cytokeratins AE1/AE3 was negative.

32.34 years, with patient ages ranging from 5 to 61 years. The prevailing site of disease was the lumbar spine (n = 27, 71%). The most common symptom mentioned by patients was pain. The mean OS of the cohort was 14.6 months.

As noted by Iacoangeli *et al*., available epidemiological data on IEES is likely unreliable, and there are currently no standardized clinical guidelines for its management in adults. Treatment approaches are often institution-specific.[31] However, the guidelines that may be most useful possible in the case of IEES are "Bone sarcomas: ESMO-PaedCan-EURACAN" of 2021.[32] In a multidisciplinary collaboration between radiologists, pathologists, and surgeons working at a bone sarcoma reference center, new cases of bone tumors should be discussed. To evaluate the extent of the diseases, examinations such as bone scintigraphy and chest CT for general staging should be done. For staging, whole-body MRI or [18F] 2- fluoro-2-deoxy-D-glucose PET-CT or PET-MRI are used more frequently.

The EE99 R3 study on primary disseminated multifocal ES identified several additional prognostic factors, including age at diagnosis (under 14 years), primary tumor volume >200 mL, the presence and number of bone lesions, additional pulmonary metastases, and bone marrow involvement. These factors were used to develop a more sensitive prognostic scoring system.[33] Renal, cardiac, and auditory dysfunction is a consequence/side effect of ChT. Therefore, before starting the treatment, it is essential to conduct baseline tests for renal and cardiac function and perform an audiogram (especially if platinum-based drugs are used). Standard ChT protocols typically include combinations of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide.[20] Neoadjuvant ChT is strongly recommended, as moderate evidence supports its benefits in improving local control and long-term survival. Present trials consist of 3–6 cycles of initial combination ChT following biopsy, followed by local therapy, and an additional 6–10 cycles of ChT, typically administered at 2–3-week intervals. The total duration of the treatment is 10–12 months.

Local RT, with doses ranging from 30 to 54 Gy, may help prevent distant recurrence. Adjuvant RT is the preferred treatment for patients with non-sacral pelvic ES, regardless of surgical margins, tumor volume, or histological response. It has been shown to offer better local control and survival outcomes compared to surgery alone. Patients who received RT show a trend toward improved survival, although this effect is not statistically significant. RT may be particularly beneficial when adequate surgical margins cannot be achieved. However, caution is warranted with radiation therapy, as sarcomas secondary to RT after ES may develop in a dose-dependent manner. On the other hand, irradiating the lungs in patients with lung metastases may provide a survival advantage.

Primary IEES is more aggressive and carries a worse prognosis compared to its osseous counterpart,[23] appearing to be similar to conventional ES with metastases. Chihak *et al*. demonstrated that IEES has a median recurrence time of 18 months and a 58% 2-year event-free survival rate, despite multimodal therapy.[19] Other studies have reported a median progression-free survival of 12 months and OS of 14 months. Factors such as large tumor size, axial location, presence of metastases at the time of diagnosis, and positive surgical margins are all associated with poor overall survival. The influence of age on the prognosis of IEES is currently debated. These figures show that IEES has a worse prognosis compared to osseous ES.

Doxorubicin treatment is no longer recommended in relapsing ES, due to previously attained total doses. At this juncture, there is no standardized ChT treatment plan, and therefore substances such as alkylating agents

Table 1: Summary of reported cases of primary IEES.

Authors	Age	Sex	Location	EWS/ FLI-1	Surgery	CT	RT	PFS	OS	Outcome
Hisaoka *et al.*[34]	14	M	D12-L2	+	GTR	NA	NA	3 m	3 m	Alive
Isotalo[35]	52	M	L2-L5	NA	GTR	NA	CS	12 m	12 m	DF 1 m
Uesaka *et al.*[36]	11	F	C7-D1	NA	STR	NA	NA	NA	NA	NA
Akyüz *et al.*[37]	31	F	L1-S2	NA	STR	VCR, CCNU, CDDP	local	2 m	4 m	DOD 4 m
Mobley *et al.*[3]	32	M	L2-L4	+	STR	Act-D+VDC/IE	local	8 m	12 m	DOD 12 m
Haresh *et al.*[4]	26	M	D11-S2	NA	GTR	VAC, ICE	Local	2 m	8 m	AWD 8 m
Kim and Shin[5]	32	F	C3-C5	NA	STR	IE	Local	12 m	12 m	DF 12 m
Klimo *et al.*[6]	10	M	L4-S2	NA	STR	VDC/IE	Local	12 m	12 m	DF 12 m
Yan *et al.*[7]	10	M	C2-C3	NA	GTR	-	-	1 m	1 m	DOD 1 m
Vincentelli *et al.*[8]	40	F	D11-L4	+	STR	DXR, holoxan	Local	6 m	6 m	DF 6 m
Duan *et al.*[9]	8	M	L2-L4	NA	+	NA	NA	NA	NA	Alive
Duan *et al.*[9]	25	M	L2-L3	NA	+	NA	NA	6 m	6 m	AWD 6 m
Karikari *et al.*[10]	56	F	L1	+	GTR	VDC/IE	NA	NA	NA	DF
Pancucci *et al.*[11]	55	M	L4-S2	+	GTR	VIDE	Local	13 m	13 m	DF 13 m
Pancucci *et al.*[11]	25	F	L2-L3	+	GTR	-	-	14 m	14 m	Alive
Khalatbari *et al.*[12]	28	F	L5-S1	+	GTR	VDC/IE	local	72 m	72 m	DF 72 m
Bazzocchi *et al.*[13]	44	F	D6-D7, L1-L2	NA	GTR	VDC/IE	Local	31 m	31 m	AWD 31 m
Huang *et al.*[14]	39	F	C4-C6	NA	GTR	VCR, THR, CTX	Local	36 m	36 m	Alive
Lozupone *et al.*[15]	44	F	L1-S3	NA	GTR	VDC/IE	Local	6 m	6 m	DF 6 m
Zhao *et al.*[16]	14	M	L2-S1	NA	STR	VDC	Local	NA	12 m	DF 12 m
Bostelmann *et al.*[17]	29	M	C7	+	GTR	VCR, IFO, DXR, VP-16	-	1 m	NA	DF 18 m
Kartal and Akatlı[18]	5	M	D4-D7	NA	STR	NA	NA	NA	NA	NA
Chihak *et al.*[19]	50	M	D10-L1	+	GTR	VDC/IE	Local	48 m	60 m	DOD 60 m
Chihak *et al.*[19]	60	M	L2-L3	+	Partial	IE/AI	Local	11 m	48 m	DOD 48 m
Chihak *et al.*[19]	25	M	C4-C7	+	STR	VDC/IE	Local	NA	20 m	DF 20 m
Chihak *et al.*[19]	34	M	L4-L5, S1-S2, S4-S5	+	Biopsy	VDC/IE	CS	3 m	3 m	DF 3 m
Scantland *et al.*[20]	14	F	L2-L3	+	STR	VDC/IE	Local	24 m	24 m	DF 24 m
Paterakis *et al.*[21]	31	M	L2-L3, L5	+	Partial	CPA, VCR, ADR, Act-D, IFO, VP-16	-	24 m	42 m	Alive
Takami *et al.*[38]	61	M	L1-L3	+	GTR	VDC/IE	Local	NA	NA	Alive
Tan *et al.*[22]	34	F	C4-T3	+	Partial	-	CS	9 m	11 m	DOD 11 m
Yan *et al.*[23]	60	M	D12-L3	-	GTR	+	-	NA	NA	NA
Izubuchi *et al.*[24]	35	F	D12-L1, L4-L5	+	STR	VDC/IE	CS	10 m	16 m	DOD 16 m
Murray *et al.*[25]	45	M	L5-S2	+	GTR	+	Local	NA	NA	NA
Pu *et al.*[26]	32	M	D12-L2	+	GTR	VAC/IE	Local	17 m	17 m	DF 17 m
Ebrahimi *et al.*[27]	13	M	L1-L2	+	GTR	NA	NA	NA	NA	NA
Praveen *et al.*[28]	23	M	L1-L2	+	GTR	+	Local	6 m	NA	NA
Shihadeh *et al.*[29]	24	M	C7-D1	+	STR	VAC/IE	Local	6 m	7 m	DOD 7 m
Salama *et al.*[30]	58	M	L3-S1	+	GTR	VAC/IE	Local	13 m	14 m	AWD 14 m
Current study	36	M	L2-L5	+	Partial	DXR+CPA	-			

NA: Not available, AWD: Alive with disease, DF: Disease free, DOD: Dead of disease, GTR: Gross total resection, STR: Subtotal resection, VCR: Vincristine, CDDP: Cisplatin, DXR: Doxorubicin, IFO: Ifosfamide, CPA: Cyclophosphamide, VP-16: Etoposide, Act-D: Actinomycin D, VDC: VCR+DXR+CPA, IE: IFO+VP-16, M: Male, F: Female, CS: Craniospinal, PFS: Progression-free survival (months), OS: Overall survival (months), IEES: Intradural extramedullary Ewing sarcoma, CT: Computed tomography, RT: Radiotherapy.

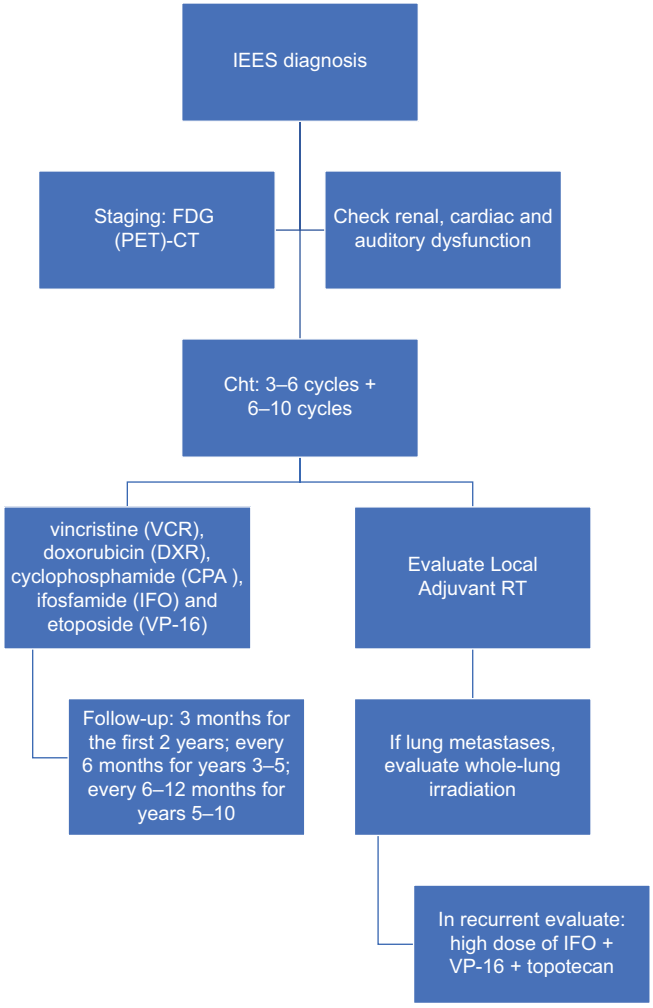

Figure 3: Flowchart of intradural extramedullary Ewing sarcoma management. VCR: Vincristine, CDDP: Cisplatin, DXR: Doxorubicin, IFO: Ifosfamide, CPA: Cyclophosphamide, VP-16: Etoposide, FDG (PET): Fluorodeoxyglucose - positron emission tomography, RT: Radiotherapy, IEES: Intradural extramedullary Ewing sarcoma.

(cyclophosphamide and high-dose ifosfamide) in combination with topoisomerase inhibitors (etoposide and topotecan), irinotecan with temozolomide or gemcitabine and docetaxel, or high-dose ifosfamide or carboplatin with etoposide are used.

Identifying local recurrence or metastases early during follow-up is important for increasing treatment success. For that reason, after completing ChT checks are suggested every 3 months for the first 2 years; every 6 months for 3–5 years; and every 6–12 months for 5–10 years.

As shown above, there is no standard protocol for IEES in the literature. However, we present a schematic flowchart that collects current management knowledge in IEES so as to be useful in daily clinical practice [Figure 3].

CONCLUSION

Despite advances in treatment modalities, the risk of local recurrence and distant metastasis underscores the need for radical surgery whenever achievable, close surveillance, and continued research to improve therapeutic strategies and outcomes for this rare entity. Primary IEES is an extremely rare condition with a similar presentation to spinal cord tumors. Available epidemiology is unreliable and therefore down to the present day, standard clinical guidelines for treatment are non-existent. Accordingly, multidisciplinary collaboration in specialty centers for bone sarcoma is pivotal for successful care. Neoadjuvant ChT as well as RT in addition to surgery are suggested. Follow-ups are crucial for early discovery of local-recurrences or metastases and contribute to improving long-term survival. Further studies are needed to portray primary IEES and postulate clinical guidelines for successful treatment.

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