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Primary Intradural Extramedullary Ewing Sarcoma of spine: Systematic Review of Literature

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ABSTRACT

Introduction

The incidence of extraosseous Ewing sarcoma, a highly malignant mesenchymal tumor, is rare in the spinal cord and its clinical outcomes unknown. To date, few cases of primary intradural extramedullary Ewing sarcoma (PIEES) have been reported in the literature, with few follow-ups.

Material and Methods

Here, we aimed to perform a comprehensive review of all cases published in the literature and update previously reported cases with our single institution case. Institutional medical records were searched for cases of PIEES of the spine managed at our institution between the years 2017 and 2023. We performed a systematic search of two electronic databases (PubMed and Medline) from inception to December 2023 to obtain all published cases of PIEES. We used our institutional medical records to update cases reported from our institution.

Results

We identified a total of 40 cases with PIEES reported in the existing literature. Of the 41 cases, the median age of diagnosis was 31 years. The most common presentation pattern was PIEES in the lumbar/sacral region (61%, n = 27), with a majority (59%, n = 25) presenting initially with pain. The most common modality of treatment reported was surgery (41/41, 100%), followed by adjuvant chemotherapy (31/41, 75%) and local radiation therapy (29/41, 70%). Overall, recurrence was reported in 17/41 (34%) cases, with median progression free survival (PFS) of 12 months (range, 1–72). There were 12/37 (29.4%) deaths reported, with median overall survival (OS) of 14 months (range, 1–72).

Conclusion

We presented the most updated review of all reported cases of PIEES. While surgical resection is the mainstay of treatment, tumor recurrence is a great concern given the adhesive nature of the lesion preventing complete resection. Adjuvant chemotherapy and radiotherapy should be carefully considered to prevent recurrence and improve survival outcome.

Key-words: primary intradural extramedullary tumor, Ewing sarcoma, adjuvant chemotherapy.

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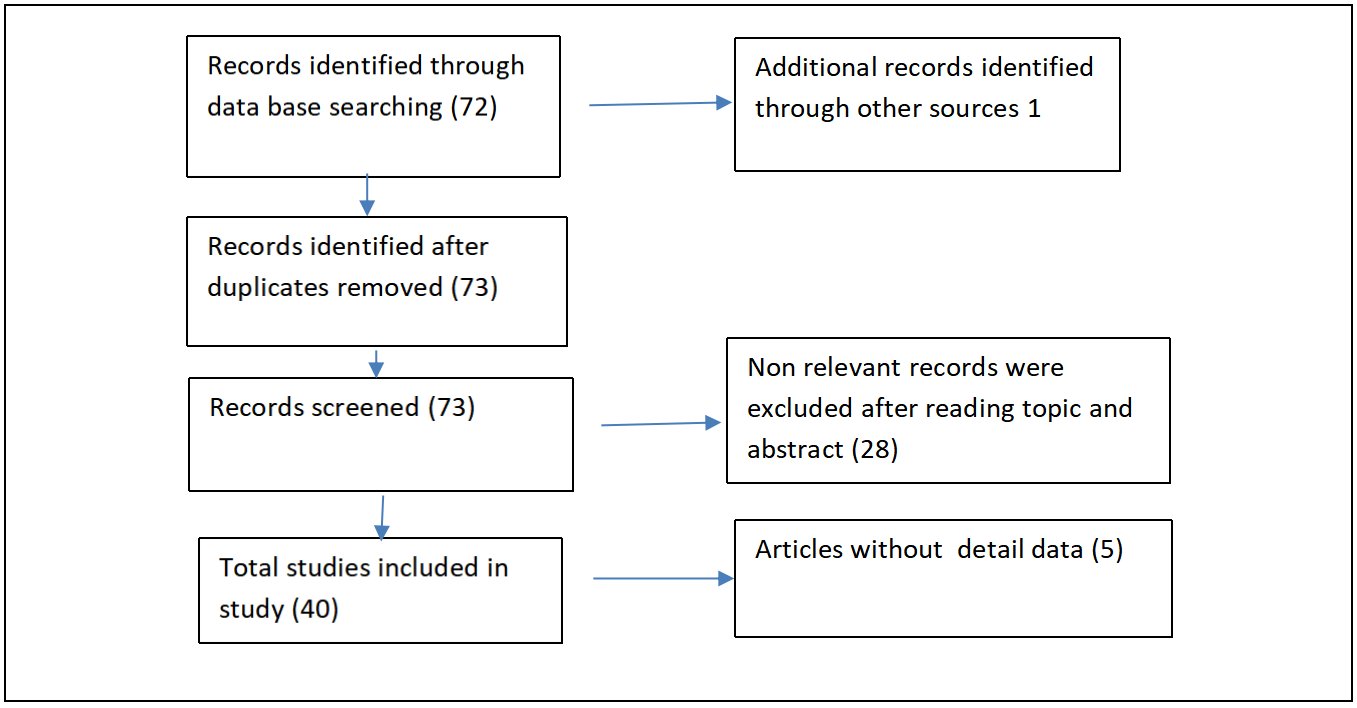
INTRODUCTION

Tumors of the spinal cord and cauda equina have a wide spectrum of histology and require care with diagnosis and surgical intervention (17,39). The differential diagnosis for intradural spinal tumors includes meningioma, nerve sheath tumors such as schwannoma or neurofibroma, astrocytoma, ependymoma, and metastasis. Spinal cord and cauda equina tumors are uncommon neoplasms, and the majority is extramedullary tumors (33,34,39). Spinal involvement of extra skeletal Ewing sarcoma in the epidural space or paravertebral area is also a differential disease (15). Ewing sarcoma is an aggressive bone and soft tissue tumor that usually affects adolescents and young adults (4,12). The Ewing sarcoma family of tumors are a group of high-grade small round cell tumors, including primitive neuroectodermal tumor (PNET) and Askin tumor. Extra skeletal Ewing sarcoma is more likely to arise in axial locations, compared to Ewing sarcoma of bone (16). Most cases of Ewing sarcoma occur in the long bones, pelvis, or ribs, and rarely in extra skeletal regions such as the paravertebral or epidural space, whereas a primary intradural extramedullary Ewing sarcoma (PIEES) is extremely rare. In general, Ewing sarcoma is treated with a multimodal approach including surgery and/or focal radiotherapy, in addition to systemic chemotherapy (12). However, because of its rarity and limited evidence regarding the therapeutic aspects of PIEES, there are no standard treatment guidelines for these tumors even though the aggressive malignant tumor causes severe neurologic morbidity and mortality without appropriate treatment. In addition, the initial imaging and clinical findings of PIEES mimic those for benign intradural spinal tumors. Therefore, it is important for oncologists and neurosurgeons to be familiar with the clinical presentation and evaluation of PIEES. Here, we describe a case of PIEES, and we present a literature review of the management and clinical course of this type of tumor.

Materials and Methods

Following Institutional Review Board approval, we conducted a systematic review of the literature in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.We searched our institutional medical records from 2017 to December 2023 for histopathologically confirmed cases of primary intradural extraosseous Ewing sarcoma or peripheral primitive neuroectodermal tumor in any age group. Cases with osseous, metastatic, extradural, or intramedullary disease at the time of diagnosis were excluded. Additionally, we systematically searched PubMed and Medline databases from inception to December 2023 using a combination of the following keywords: intradural, Ewing sarcoma or peripheral primitive neuroectodermal tumor, extramedullary, spinal cord, spine. Two authors independently reviewed all cases to assess eligibility for inclusion (FIGURE 3).

FIGURE 3:Flowchart of selection process to enrol eligible studies



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RESULTS

Clinical presentation and surgical management of our case

A 38-year-old female presented with complaints of pain in the lower back, radiating to the left lower limb, Associated with tingling and numbness. Pain was insidious in onset and progressive. There was no associated fever, weight loss, bowel and bladder symptoms, or any sensory or motor deficit. The sensory system was intact in that limb. Magnetic resonance imaging (MRI) scan of the lumbosacral spine showed an intradural extramedullary space occupying lesion, 11x8mm in size, extending from L2 to L3 vertebral region (Figure 1A-C). It caused displacement and compression of the lumbar nerve roots at cauda equina. The patient underwent L2–L3 laminectomy with excision of the lesion on October 30, 2021. Histopathological examination revealed a monomorphic population of round cells with moderate amounts of clear to eosinophilic cytoplasm and central nucleus. Intermixed with these cells there are stromal fragments and neurofibrillary material with occasional foci of pseudo-rosettes (Figure 1D). In view of the location Suggestive of a small blue round cell tumor. IHC revealed positive for CD 99 and FLI-1 strongly suggestive of PNET. Synaptophysin and BCL-2 expression can be seen in Ewing sarcoma. The hospitalization of the patient was uneventful, and she was discharged to rehab being able to ambulate with assistance. She was subsequently followed up after 2 months with MRI whole neuroaxis (Figure 1E) and PET-SCAN which showed no lesion. Hence case concluded as primary PNET in any other area. Patient is under chemoradiotherapy now.

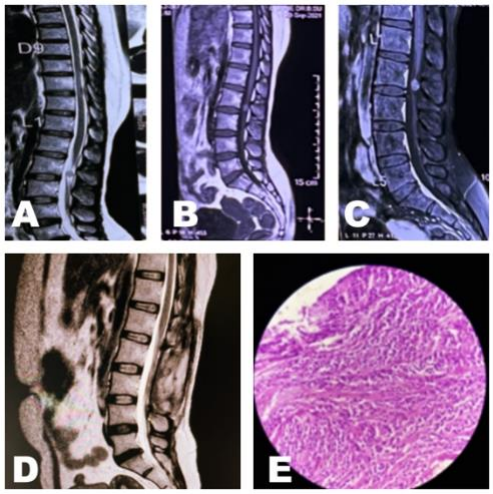

Figure 1: (A-C) Pre-operative MRI shows focal homogenous enhancing on T1WS and slightly hyperintense 11x8mm lesion on T2WS at L3-L4 level, compressing the abutting descending nerve roots likely meningioma / neurogenic lesion. (D) T2WSequence shows post-operative control with no residual lesion at L3-4. (E) Hematoxylin and eosin (H&H) staining (40X) shows small blue round cells suggestive for PNET.

Review of the literature

We identified a total of 32 papers (3,5-8,10,13-16,18-28,30-32,35-38,40-42,44) and 40 previously published cases in the literature (Table 1). Median age of diagnosis resulted in 31 years , with 70% (n = 31) male incidence. The most common location was the lumbar/sacral region 61% (n = 27), with 59% (n = 26) of patients presenting with a chief complaint of pain, and 41% (n = 18) with a chief complaint of weakness. The average duration of the chief symptom was 3 months. The most common modality of treatment reported was surgery (100%, 41/41) followed by adjuvant chemotherapy (75%, n = 31) and local radiation therapy (70%, n = 29). Gross total resection was achieved in 65% (28/ 44) of cases, and median radiation dose was 5000 to the spine. Overall, recurrence was reported in 34% (17/41) of cases, with a median progression free survival (PFS) of 12 months (range: 1–72). There were 12/41 (29.4%) deaths reported, with median overall survival (OS) of 14 months (range:1–72). Kaplan-Meier curves show OS and PFS in Figure 2.

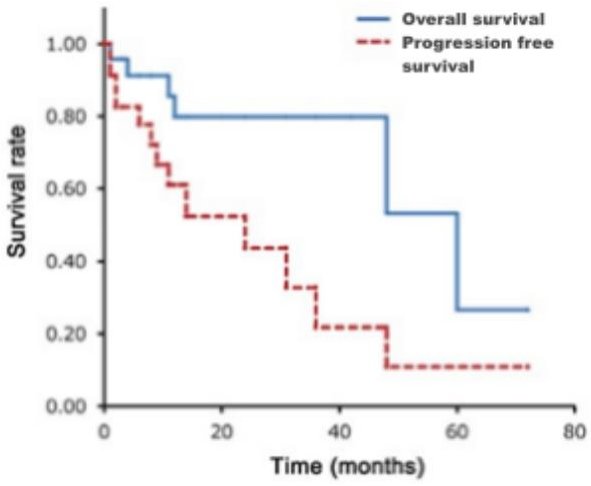

Figure 2: Kaplan-Meier curves show overall survival and progression-free survival. The 1- and 5-year overall survival rates were 79.8 % and 26.6%, respectively. The 1- and 5-year progression-free survival rates were 61.0% and 10.9%, respectively

DISCUSSION

We present an extremely rare case of PIEES. Clinical information for 41 cases of PIEES reported from 1997 to 2019 is summarized in Table I (3,5-8,10,13-16,18-28,30-32,35-38,40-42,44). Of the 41 patients, 27 were male (65%) and 14 were female (35%). The median age at diagnosis was 31 years. The lumbar-sacral region was the most common location (n=20, 66.7%), and multiple lesions viewed as meningeal dissemination were found in 8 patients (26.7%) at diagnosis. The most common chief symptom was pain (n=25, 83.3%). Motor disturbance of a lower or upper limb occurred in 15 patients (50.0%), and bladder and rectal disturbance were present in 8 patients (26.7%). Ewing sarcoma is categorized as a small round cell sarcoma with pathognomonic molecular findings and varying degrees of neuroectodermal differentiation by immunohistochemistry (1,2,29,44). Classic Ewing sarcoma lacks neural differentiation and typically has only characteristic diffuse membranous CD99 (encoded by the MIC gene) positivity (11). Almost all cases in Table I (n=28, 93.3%) showed CD99 or MIC2 positivity. Ewing sarcoma has a specific translocation involving the EWSR1 gene on chromosome 22, which produces an EWSR1-FLI1 fusion gene transcript and oncoprotein (9,10,11,13-14,35-38). RT-PCR or fluorescence in situ hybridization (FISH) can be used to detect the fusion gene, and this was detected in 16 of the reported PIEES cases. The 1- and 5-year OS rates were 79.8% and 26.6%, and the 1-, 2- and 5-year progression free survival rates were 61.0%, 52.3% and 10.9% (Figure 2). Although the Kaplan-Meier survival analysis has certain limitation because the patients in Table I had a short duration of follow-up, these results suggest that PIEES has a poorer prognosis than conventional localized Ewing sarcoma, which has a 5-year OS of 65-75%. The prognosis of PIEES was the same as that of conventional Ewing sarcoma with metastases (12). Patients with Ewing sarcoma used to receive neoadjuvant chemotherapy upon diagnosis of Ewing sarcoma by biopsy. However, spinal tumors are usually diagnosed after resection. All patients in Table I also received adjuvant chemotherapy after diagnosis. In the current case, multiagent chemotherapy was given, including VDC alternating with IE, as described above. Zhang et al (43), suggested that adults with Ewing sarcoma should be treated with adequate cycles of intensive chemotherapy at appropriate intervals. Ewing sarcoma is radiosensitive (10,13,35,40), and in our case we used whole spine radiotherapy without whole brain irradiation

CONCLUSION

We presented the most updated review of all reported cases of PIEES. While surgical resection is the mainstay of treatment, tumor recurrence is a great concern given the adhesive nature of the lesion preventing complete resection. Adjuvant chemotherapy and radiotherapy should be carefully considered to prevent recurrence and improve survival outcome.

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