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A Rare Case of Extraosseous Ewing's Sarcoma / Primitive Neuroectodermal Tumor in a Female

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KEYWORDS

Ewing's sarcoma, Soft tissue, Primitive neuro-ectodermal tumor, Small round cell, Immunohisto-chemistry.

ABSTRACT:

Introduction: Extraosseous Ewing's sarcoma [EES] is a rare form of Ewing's sarcoma that arises outside the bones in soft tissue structures. It is thought to result from a genetic abnormality involving the fusion of the EWSR1 gene with various partner genes, most commonly the FLI-1 gene. Common symptoms include pain, swelling, and sometimes a palpable mass at the site of the tumor. Diagnosis typically involves imaging studies such as magnetic resonance imaging [MRI], computed tomography [CT] scans, and biopsy for confirmation. Treatment typically includes a combination of chemotherapy, surgery to remove the tumor, and sometimes radiation therapy.

Case Presentation: In this report we present a case of Extraosseous Ewing's sarcoma in a 44 year old female who presented with the complaints of swelling in the right thigh for 3 months. The mass was soft in consistency with well delineated borders, evident both clinically and radiologically, extending into the subcutaneous layer and involving the right inguinal lymph nodes. The mass was widely excised with en-bloc dissection of the right inguinal nodes. The histopathological features confirmed the diagnosis and has been discussed in this study.

Conclusions: This case underscores the clinical significance of extraosseous Ewing's sarcoma, a rare variant presenting diagnostic challenges. Our findings highlight the importance of prompt diagnosis and early management to improve outcomes for patients with this aggressive malignancy.

1. Introduction

Ewing's sarcoma, initially described by James Ewing in 1921, is a highly aggressive tumor affecting adolescents and young adults, comprising 10% to 15% of all bone sarcomas.[1] It encompasses classic bone Ewing sarcoma, Extraosseous Ewing sarcoma, Askin tumor [malignant small cell tumor of the chest wall], and soft tissue-based primitive neuroectodermal tumors.[2]

Extraosseous Ewing sarcoma predominantly impacts young individuals and carries a poor prognosis, especially in metastatic cases, with high mortality rates. It can manifest in various locations without specific clinical symptoms, which often leads to delayed diagnosis. Definitive diagnosis relies significantly on histopathological examination due to the absence of specific clinical and radiological indicators.[4]

These sarcomas share similar histologic and immunohistochemical features, suggesting a common origin from mesenchymal progenitor cells.[2] Treatment typically involves surgical excision aimed at complete tumor removal while preserving organ function to the extent possible.[4] Despite historically high mortality rates, advancements in local therapy and multi-agent chemotherapy have substantially improved the 5-year survival rate, increasing it from less than 20% to over 70%.[2]

2. Case Presentation

A 44-year-old female with no notable pathological history was admitted with complaints of swelling in the right thigh for the past 3 months. Initially, the swelling was small and gradually progressed to the present size of approximately 5 x 4cm. It was initially painless;

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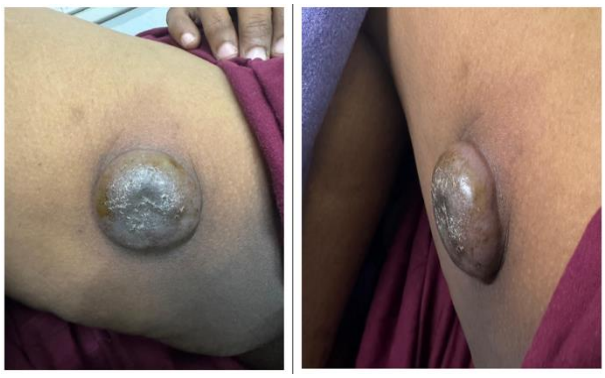
however, as the swelling progressed, it became associated with intermittent dull aching pain, with no aggravating or relieving factors reported. She denied any history of trauma, fever, discharge, or restriction of movements. Additionally, there was no history of weight loss, loss of appetite, breathing difficulties, or back pain.

The biochemical workup showed no abnormalities. Physical examination revealed a swelling approximately 5x4cm in size located in the anteromedial aspect of the right thigh, around 8cm below and lateral to the pubic tubercle and 10cm below the inguinal crease line. It appeared globular in shape with a smooth surface. The skin over the swelling was hyperpigmented and non-pinchable, while the surrounding skin appeared normal.

[Table/Figure 1] There was no local warmth or tenderness, and the swelling felt firm to hard in consistency with well-defined borders. The swelling was mobile in all directions and not fixed to the underlying muscle after contraction. It was fluctuant, irreducible, and no scar or sinus was observed over it. Ipsilateral inguinal group of lymph nodes were palpable.

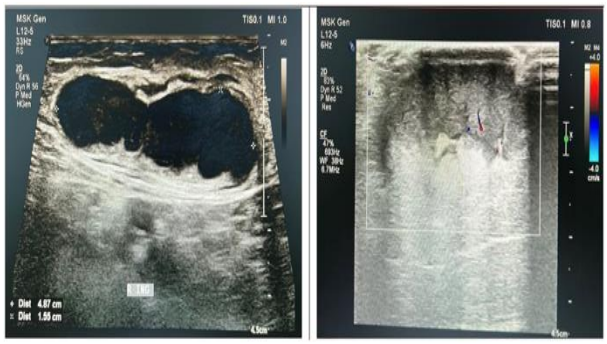


Table/Figure 1: Clinical presentation of the patient with the swelling

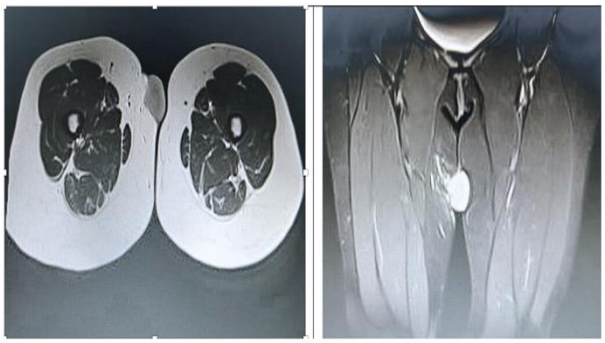
Ultrasound examination of the neck showed a well-defined ovoid heterogeneous lesion in the skin and subcutaneous aspect of upper third of right thigh in its medial aspect with vascularity seen on doppler, enlarged lymph nodes with loss of fatty hilum in the right inguinal region.

[Table/Figure 2] MRI Right thigh revealed: A well-defined STIR hyperintense, T1 hypointense T2 intermediate SI lesion measuring 3.8 x 3.0cm noted involving the subcutaneous plane of anteromedial aspect of upper one third of right thigh with surrounding STIR hyperintensities. No obvious intramuscular or underlying bone extension seen. Few tortuous vessels seen adjacent to the lesion.

Enlarged lymph nodes noted in right inguinal region, largest measuring 4.6x 1.7cm. [Table/Figure 3] Magnetic Resonance Imaging [MRI] abdomen showed right inguinal lymphadenopathy and computed Tomography [CT] chest was unremarkable.



Table/Figure 2: Ultrasonogram of the local area of right thigh swelling



Table/Figure 3: Magnetic Resonance Imaging of right thigh swelling extending till the subcutaneous layer

Fine needle aspiration cytology was performed on the swelling and lymph nodes, revealing atypical cells suggestive of malignancy and reactive lymphadenitis, respectively.

The patient underwent a wide local excision with right inguinal en-bloc dissection under spinal anaesthesia. Intraoperatively, the swelling was found to extend till the subcutaneous plane. After meticulous dissection, the great saphenous vein was ligated and divided, and the swelling was excised in toto, sparing the medial cutaneous nerve of the thigh. [Table/Figure 4]

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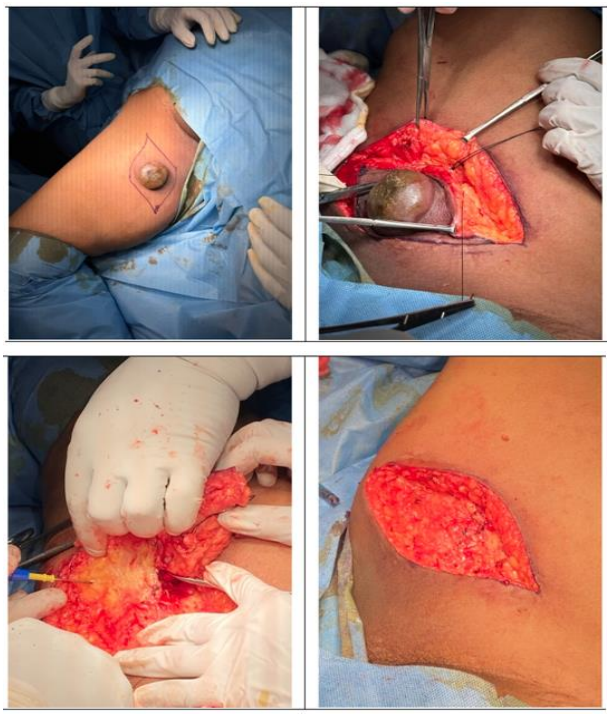
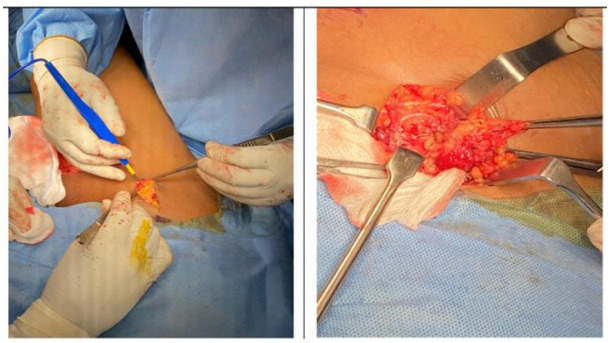


Table/Figure 4: Intra operative pictures – Excision of the swelling with ligation of GSV

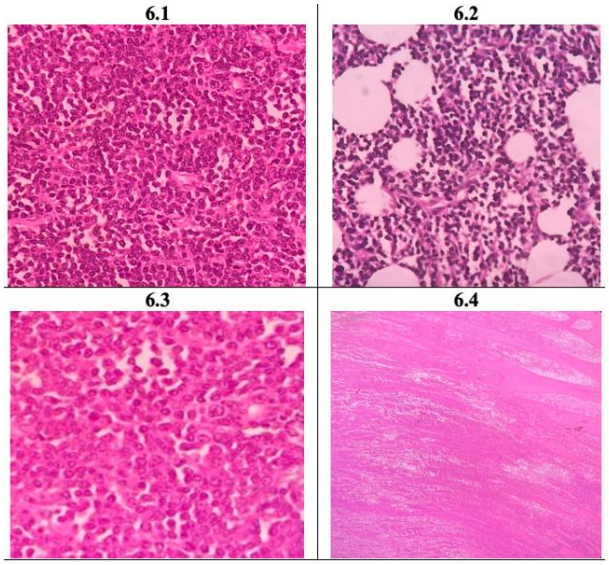
Subsequently, the right superficial inguinal nodes along the course of the great saphenous vein were identified and en-bloc dissection was performed [Table/Figure 5]. The specimen and the inguinal nodes were sent for histopathological examination. The wound was carefully closed in layers after achieving haemostasis. The postoperative period was uneventful, with no sensory or motor deficits. The patient was followed up for 2 months, had no complaints, was symptom-free, and the wound healed well.



Table/Figure 5: Intra operative pictures –

En-Bloc dissection of the right inguinal nodes

Microscopic examination studied from tumor proper showed sheets of atypical cells. Each cells have predominantly round to oval vesicular nucleus with moderate eosinophilic cytoplasm with indistinct cell borders [Table/Figure 6.1]. Tumor was present in the dermis extending into subcutaneous adipose tissue [Table/Figure 6.2]. Individual adipocytes seen trapped within sheets of tumor cells. Focal storiform arrangement of tumor cells noted [Table/Figure 6.3]. In deep dermis, tumor cells have spindle shaped nucleus with eosinophilic cytoplasm. [Table/Figure 6.4]



Table/ Figure 6: Microscopic slides of the tumor with the hematoxylin–eosin-stain

The final impression was malignant undifferentiated soft tissue sarcoma with predominantly round cell morphology. The tumor extends from the dermis and infiltrates into subcutaneous fat, with all surgically resected margins free of tumor. One of two inguinal lymph nodes shows involvement by tumor with the same morphology. Further immunohistochemical markers were performed to confirm the cell origin, revealing diffuse cytoplasmic positivity for vimentin in tumor cells, membranous positivity for CD99 and CD31 in tumor cells, and weak positivity for FLI-1, while testing negative for CD34, CD45, SMA, S100, NKX2.2, ERG, and MYOD1. This immunoprofile is suggestive of Primitive Neuroectodermal Tumor [PNET]/Ewing's Sarcoma. [Table/Figure 7]

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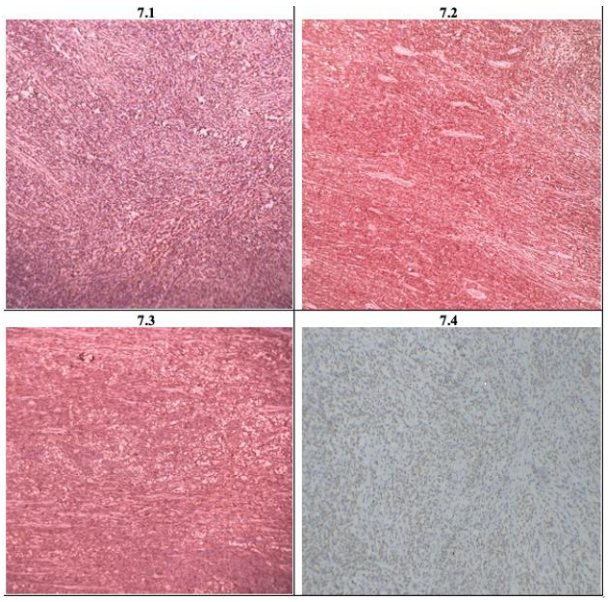

Table/ Figure 7.1: VIMENTIN POSITIVE,
Table/ Figure 7.2: CD99 POSITIVE,
Table/ Figure 7.3: CD31 POSITIVE,
Table/ Figure 7.4: FLI-1 WEAK POSITIVE

3. Discussion

Ewing's sarcoma [ES] is a highly metastatic type of sarcoma, ranking as the second most common primary malignant bone tumor, primarily affecting adolescents.[2] Although in our case it was a 44years old female. Ewing's sarcoma family tumors are characterized by non-random chromosomal translocations that generate fusion genes encoding abnormal transcription factors. The t[11;22][q24;q12] translocation, found in 85% of cases, results in the formation of EWS-FLI-1. In contrast, the t[21;12][22;12] translocation leads to the less common EWS-ERG fusion, present in 10% to 15% of cases.[6] Primitive neuroectoderm tumor [PNET], these tumors are believed to originate from fetal neuroectodermal cells and exhibit small-round-cell morphology with varying degrees of neural, glial, and ependymal features.[12] PNETs are categorized into central and peripheral types based on their cell of origin and location [16]

It is widely acknowledged that Ewing's sarcoma [EWS] and peripheral primitive neuroectodermal tumor [pPNET] represent a unified neoplastic process, as evidenced by their overlapping morphological features, including ultrastructure, immunophenotype, and a shared set of molecular genetic abnormalities [7, 8]. This neoplasm is now termed EWS/pPNET, which is the preferred terminology according to the World Health Organization classification of soft tissue and bone tumors [9], or alternatively, the Ewing family of tumors. These tumors originate from unique mesenchymal stem cells capable of differentiating into osteogenic, adipogenic, or neurogenic lineages. They exhibit a spectrum of behaviour ranging from indolent to highly invasive and metastatic [1,11].

Ewing's sarcoma commonly affects anatomical sites such as the pelvis, axial skeleton, and femur; however, it can arise in almost any bone or soft tissue. Typically, patients present with pain and swelling at the affected site.[2] Despite its propensity for local spread, Extraosseous Ewing sarcoma [EES] usually exhibits a pseudo capsule, which gives it a well-defined appearance on computed tomography [CT] scan or magnetic resonance imaging [MRI].

Several diagnostic approaches are employed for confirming EWS/PNET. The first approach involves examining tumor tissue under light microscopy, including immunohistochemistry. These tumors are composed of primitive-looking round cells with a high nucleus-to-cytoplasm ratio.[16]A variety of immunohistochemical markers are utilized in the study of Extraosseous Ewing sarcoma [EES]. These markers encompass the CD99 antigen, known for its high sensitivity though lack of specificity, and FLI1, which offers greater specificity compared to CD99. Molecular genetic analysis involves fluorescence in situ hybridization, which is considered indispensable. Immunohistochemical staining typically reveals diffuse positivity for CD99 (MIC2), FLI-1, and vimentin.[17] Detection of the MIC2 gene through CD99 staining strongly suggests Extraosseous Ewing sarcoma [EES]. In our case there is strong positivity for CD99, vimentin, and weak positivity for FLI-1.

Radical excision surgery is considered the gold standard of treatment. Margin-negative surgery is crucial as there is no potential cure in sarcoma patients without achieving it.[16] Chemotherapy follows surgery to improve overall survival rates and reduce the risk of tumor recurrence [14], using a combination of multiple agents to enhance response rates.[15] Initially, regimens included vincristine, cyclophosphamide, actinomycin D, and doxorubicin (VAcCD). Ewing's sarcoma can be

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complicated by metastases, local recurrence, secondary malignancies, pathological fractures, and morbidities associated with surgery, radiation, and chemotherapy.

4. Conclusion

Ewing's sarcoma are highly malignant tumors characterized by small, round cells originating from the neuroectoderm of bone and soft tissue. The exact histogenesis remains uncertain, but it is likely that the tumor cells arise from primitive mesenchymal cells with potential for limited neural differentiation. Biopsy is essential for a definitive diagnosis, with commonly utilized techniques being open biopsy or imaging-guided core biopsy. Immunohistochemical and genomic studies play a crucial role in achieving accurate diagnosis. Modern therapy for EES follows the standard approach for all sarcomas in the Ewing family, involving chemotherapy for systemic disease control followed by extensive surgical resection and/or radiation for local disease control. Prognosis in Ewing's sarcoma varies based on factors such as tumor size and location, presence of metastasis, and response to treatment.

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