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EWING SARCOMA- CLUES IN THE BLUES

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ABSTRACT

Background: Ewing sarcoma, a rare and aggressive malignancy, ranks as the second most common pediatric bone tumor, with extraskeletal presentations being less frequent, particularly in adults. Its diverse clinical and anatomical manifestations pose significant diagnostic challenges, necessitating comprehensive evaluation to differentiate it from other small round blue cell tumors. **Aim:** To characterize the clinical, radiographic, histopathologic, and immunohistochemical features of classical and extraskeletal Ewing's sarcoma in a 14-patient cohort, emphasizing diagnostic approaches and differential considerations.

Materials and Methods: This retrospective case series analyzed 14 patients diagnosed at the Institute of Pathology, Madras Medical College, Chennai, India, from January 2023 to May 2024. Diagnosis was confirmed through clinical assessment, imaging (X-ray, CT, MRI, ultrasonography), histopathology (hematoxylin and eosin), and immunohistochemistry (CD99, FLI-1, Tdt, MyoD1, CD45, Desmin, SATB2, SMA, CK, S100, TLE, ERG) on formalin-fixed paraffin-embedded tissues. Data on demographics, tumor site, clinical presentation, and diagnostic findings were collected and descriptively analyzed.

Results: The cohort consisted of 14 patients (10 males, 4 females), aged between 7 and 70 years. Of these, 8 cases (57.1%) were classical (bone-based) and 6 cases (42.9%) were extraskeletal in origin. Clinical symptoms included pain in 13 patients (92.8%), swelling or palpable mass in 9 patients (64.3%), and pulmonary metastases at diagnosis in 4 patients (28.6%). Imaging revealed osteolytic lesions with periosteal reactions in classical cases, while extraskeletal cases showed heterogeneous soft tissue masses. All tumors exhibited small round blue cell morphology. Immunohistochemically, 13 out of 14 cases (92.8%) showed diffuse membranous CD99 positivity (>80–90%) and all cases (100%) were positive for FLI-1 (>90%), aiding in the differentiation from mimics such as lymphoma and rhabdomyosarcoma.

Conclusion: This series underscores the diverse anatomical presentations of Ewing sarcoma and highlights the pivotal role of immunohistochemistry in achieving accurate diagnosis, especially in extraskeletal forms. The integration of clinical, radiologic, and histopathologic features in a multidisciplinary framework is essential for timely recognition and improved management of this aggressive malignancy.

MeSH Keywords: Ewing Sarcoma; Sarcoma, Extraskeletal; Immunohistochemistry; CD99 Antigen; FLI-1 Protein; Small Round Blue Cell Tumor.

INTRODUCTION

Ewing sarcoma, first described by James Ewing in 1921, is a rare and aggressive malignant neoplasm that predominantly affects children and young adults. It constitutes approximately 10–15% of all primary malignant bone tumors and remains the second most common bone malignancy after osteosarcoma in the pediatric population. Although it commonly arises in bones such as the pelvis, femur, tibia, and ribs, a significant proportion of cases—especially in adults—occur in soft tissues, referred to as extraskeletal Ewing sarcoma. Extraskeletal variants are notably rarer, with an incidence estimated at 0.4 per million population per year, and tend to present with more advanced disease due to their subtle clinical features and anatomically diverse locations, often delaying diagnosis and impacting survival outcomes adversely.[1]

The diagnosis and management of extraskeletal Ewing sarcoma remain challenging due to its nonspecific clinical manifestations and radiographic ambiguity. Unlike classical osseous Ewing sarcoma, which typically presents with localized bone pain, swelling, and characteristic radiologic findings such as lytic lesions with periosteal reactions, the extraskeletal form may occur in virtually any soft tissue, leading to atypical symptomatology and frequent misdiagnosis. Moreover, its histologic resemblance to other small round blue cell tumors further complicates the diagnostic process.[1] Abboud *et al.* noted that extraskeletal forms of this tumor are often under-recognized in early clinical encounters, especially when arising in unusual sites such as the thoracic wall, paravertebral tissues, or retroperitoneum, and emphasized the need for a multidisciplinary approach to improve outcomes.[1]

Feng *et al.* described a series of eight cases of Ewing sarcoma involving the jaw, underscoring the diagnostic complexity associated with craniofacial involvement.[2] The authors noted that such presentations are frequently mistaken for odontogenic infections or other benign maxillofacial tumors, especially in settings where radiological and pathological correlation may be delayed. In their series, imaging often revealed nonspecific lytic lesions or soft tissue expansion without definitive cortical disruption, necessitating histopathologic confirmation and immunohistochemical validation. The lack of classical radiographic signs, such as the "onion-skin" appearance or Codman's triangle, in extraskeletal forms means that reliance on imaging alone is insufficient for accurate diagnosis.[2]

A growing body of literature has explored the genetic and molecular profile of Ewing sarcoma, highlighting specific chromosomal translocations that underpin its pathogenesis. Tsuda *et al.* identified a subset of Ewing sarcomas characterized by rearrangements involving the FEV gene, which were strongly associated with extraskeletal locations and exhibited particularly aggressive clinical behavior.[3] These tumors, despite sharing histologic similarities with classical Ewing sarcoma, were found to exhibit greater resistance to conventional chemotherapy and more frequent early metastases, particularly to the lungs and bone marrow. Their findings suggest that molecular profiling is vital not only for diagnosis but also for prognostication and therapeutic planning in atypical cases.[3]

Biomarker identification has significantly improved the specificity of Ewing sarcoma diagnosis. Daher *et al.*, in a systematic review, reported that while CD99 expression remains a cornerstone in the diagnostic algorithm, its nonspecificity necessitates the inclusion of other markers such as FLI-1, NKX2.2, and ERG, especially when distinguishing from lymphoblastic lymphoma, rhabdomyosarcoma, or neuroblastoma.[4] They emphasized that while FLI-1 expression is seen in the majority of Ewing sarcomas, its absence does not exclude the diagnosis, particularly in molecular subtypes with non-FLI-1 translocations. Furthermore, the review highlighted the emerging role of molecular diagnostics in refining differential diagnoses and underscored the urgent need for standardization of diagnostic panels across centers dealing with rare sarcomas.[4]

Brown *et al.*, analyzing a cohort of patients with pelvic Ewing sarcoma, demonstrated the anatomical site to be a key determinant of prognosis.[5] The deep-seated location and proximity to vital structures often preclude wide-margin resections, leading to suboptimal local control. In their study, patients with pelvic primaries had significantly lower overall survival compared to those with extremity involvement. This trend is amplified in extraskeletal sarcomas, where organ involvement, anatomical constraints, and late presentation further complicate both surgical and chemotherapeutic management.[5]

Grünewald *et al.*, in a landmark review, outlined the histopathologic characteristics of Ewing sarcoma, reaffirming that both classical and extraskeletal variants display small round blue cell morphology, scant cytoplasm, and high nuclear-cytoplasmic ratios [6]. Their study consolidated decades of research on the neuroectodermal origin of this malignancy, linking its phenotype to primitive mesenchymal stem cells with neural differentiation potential. They also explored therapeutic advancements such as IGF-1R inhibition, PARP inhibitors, and CDK4/6 blockers, which are being investigated as targeted therapies for resistant or metastatic disease. Despite these innovations, the 5-year survival rate for metastatic Ewing sarcoma remains dismal, often below 30%, reinforcing the critical importance of early and accurate diagnosis.[6]

Gaspar *et al.* conducted a multinational collaborative study that analyzed current management strategies and future directions in Ewing sarcoma through data consolidation from

multiple oncology groups.[7] Their study underscored the value of early multimodal therapy—including neoadjuvant chemotherapy, local control by surgery and/or radiotherapy, and maintenance chemotherapy—as the cornerstone of improved survival. However, they acknowledged that clinical trials for extraskeletal forms remain limited due to the rarity of these presentations. They advocated for registries and multinational trials to collect data on atypical Ewing sarcoma cases and facilitate evidence-based treatment planning, especially in low-resource settings where molecular diagnostics are not universally available.[7]

Machado *et al.* highlighted the emergence of new Ewing-like sarcomas, particularly those with CIC and BCOR rearrangements, which exhibit histologic and immunohistochemical overlap with classical Ewing sarcoma but differ in molecular signature and clinical outcome.[8] Their review emphasized that these entities should not be considered true Ewing sarcomas, given their distinct genetic background and poor response to Ewing-specific chemotherapy. Differentiation between Ewing sarcoma and its mimics is imperative for appropriate treatment and counseling. The increasing recognition of these variants further justifies comprehensive IHC and molecular testing for all small round blue cell tumors of childhood and young adulthood.[8]

Riggi *et al.* provided a comprehensive overview of Ewing sarcoma, detailing its pathophysiology, transcriptional regulators, and oncogenic drivers.[9] They explained how the EWS-FLI1 fusion protein acts as an aberrant transcription factor, reprogramming mesenchymal stem cells and driving tumorigenesis. This molecular insight has led to the development of novel experimental therapeutics targeting EWS-FLI1-driven pathways. Although these agents are still in early-phase trials, their application may hold promise in improving outcomes for patients with chemoresistant or metastatic disease. Moreover, understanding the fusion transcript landscape has aided in differentiating Ewing sarcoma from other round cell tumors, especially in ambiguous cases.[9]

Kennedy *et al.* presented a unique case report of extraskeletal Ewing sarcoma involving the spine and discussed the associated diagnostic and therapeutic difficulties.[10] Their findings paralleled many of the modern challenges associated with EES, particularly in adults and elderly individuals where soft tissue sarcomas are not commonly suspected. The case reinforced the role of cross-sectional imaging, image-guided biopsy, and the essential utility of immunohistochemistry in delineating such lesions from more common adult soft tissue tumors.[10]

Given the global burden, expanding clinical spectrum, molecular diversity, and persistent diagnostic challenges associated with Ewing sarcoma—especially in its extraskeletal forms—there is a compelling need to document and analyze such cases in a structured, multidisciplinary framework. This study addresses that gap by presenting a series of cases diagnosed at a tertiary care center in South India, highlighting the critical role of histopathology and immunohistochemistry in early detection, especially when molecular tools are inaccessible. It aims to improve awareness, refine diagnostic strategies, and contribute valuable data on rare anatomical sites, adult presentations, and histologic mimics in the evolving landscape of Ewing sarcoma.

MATERIALS AND METHODS

This retrospective case series, conducted at the Institute of Pathology, Madras Medical College, Chennai, India, evaluated 14 patients diagnosed with Ewing's sarcoma between January 2023 and May 2024. The patient data were anonymized. The inclusion criteria encompassed histopathologically confirmed classical (skeletal) or extraskeletal Ewing sarcoma diagnosed through clinical, radiographic, and immunohistochemical (IHC) assessments. Patients with incomplete diagnostic records were excluded.

Clinical data, including age, sex, symptoms, and tumor site, were retrieved from medical records, noting presentations such as pain and swelling. Imaging modalities (X-ray, CT, MRI, ultrasonography) were used to characterize tumor features, including osteolytic lesions or soft tissue masses. Histopathological analysis was performed on formalin-fixed, paraffin-embedded tissues using hematoxylin and eosin (H&E) staining for morphology. IHC utilizes a panel of markers (CD99, FLI-1, Tdt, MyoD1, CD45, Desmin, SATB2, SMA, CK, TLE, ERG, S100) to verify the diagnosis and exclude mimics such as lymphoma or rhabdomyosarcoma. Extraskeletal cases were identified based on their soft-tissue origin.

Data were descriptively analyzed to summarize the clinical, radiographic, histopathological, and IHC findings, and the cases were categorized as classical or extraskeletal. No statistical analysis was conducted due to the descriptive design. The diagnostic protocol followed established guidelines to differentiate Ewing sarcoma from other small round blue cell tumors, ensuring a multidisciplinary approach to diagnosis.

CASE PRESENTATIONS

This case series details 14 patients diagnosed with Ewing sarcoma at the Institute of Pathology, Madras Medical College, Chennai, India, from January 2023 to May 2024. The cohort, comprising 10 males and 4 females aged 7–70 years, includes eight classical (skeletal) and six extraskeletal cases. Each case is presented with clinical history, radiographic findings, histopathologic features, and immunohistochemical (IHC) results, highlighting diagnostic challenges.

Classical Ewing's Sarcoma Cases

Case 1: 26-Year-Old Male, Costophrenic Mass

A 26-year-old male with a prior history of excised primitive neuroectodermal tumor presented with a left costophrenic mass, without respiratory symptoms. Contrast-enhanced CT (CECT) revealed a heterogeneous soft tissue lesion (8.1 × 7.1 × 3.1 cm) in the left costophrenic sulcus with thickened pleura but no Evident rib erosion. A CT-guided biopsy showed a small round blue cell morphology. IHC demonstrated CD99 (>80%) and FLI-1 (>90%) positivity, with negative MyoD1, NSE, CD34, OCT3/4, PLAP, and PANCK, supporting a diagnosis of classical Ewing sarcoma.

Case 2: 7-Year-Old Male, Ulna

A 7-year-old male presented with a 3-month history of pain and swelling in the right forearm. Radiography revealed an osteolytic lesion with a periosteal reaction in the proximal ulna. Histopathology of the biopsy showed a small round blue cell tumor. IHC demonstrated CD99 and FLI-1 positivity, with negative CD45 and MyoD1, excluding lymphoma and rhabdomyosarcoma, establishing classical Ewing sarcoma.

Case 3: 15-Year-Old Male, Maxilla

A 15-year-old male presented with a 4-month history of facial swelling and pain in the right maxilla. CT revealed a lytic lesion with soft tissue extension. Biopsy histopathology showed a small round blue cell tumor. IHC demonstrated strong CD99 and FLI-1 positivity, with negative MyoD1 and CD45, confirming classical Ewing sarcoma.

Case 4: 22-Year-Old Male, Femur

A 22-year-old male presented with a 6-month history of thigh pain and limited movement. Radiography revealed an osteolytic lesion in the distal femur, and MRI confirmed a soft tissue mass. Histopathology of the biopsy showed a small round blue cell tumor. IHC demonstrated CD99 and FLI-1 positivity, with negative Desmin and CD45, confirming classical Ewing sarcoma.

Case 5: 30-Year-Old Female, Rib

A 30-year-old female presented with a 5-month history of chest pain and a palpable mass. CT revealed an osteolytic lesion in the right sixth rib. Biopsy histopathology showed a small round blue cell tumor. IHC demonstrated CD99 and FLI-1 positivity, with negative MyoD1 and CD45, establishing classical Ewing sarcoma.

Case 6: 40-Year-Old Male, Pelvis

A 40-year-old male presented with a 7-month history of pelvic pain and swelling. CT revealed a lytic mass in the right pelvis. Histopathology of the biopsy showed a small round blue cell tumor. IHC demonstrated CD99 and FLI-1 positivity, with negative SMA and Desmin, confirming classical Ewing sarcoma.

Case 7: 13-Year-Old Male, Clavicle

A 13-year-old male presented with a 5-month history of progressive swelling and pain at the medial end of the right clavicle. Physical examination revealed a firm, tender mass without systemic symptoms. Radiography demonstrated an osteolytic lesion in the medial third of the clavicle, and MRI confirmed a lytic destructive mass (3 × 4.3 × 4 cm) with soft tissue extension. Curettage was performed, and histopathology revealed a small round blue cell tumor with uniform cell morphology. IHC showed diffuse CD99 (>90% membranous) and strong FLI-1 (>90% nuclear) positivity, with occasional Tdt positivity and negative CD45, CD1a, and MyoD1, ruling out lymphoma and rhabdomyosarcoma, confirming classical Ewing sarcoma.

Case 8: 17-Year-Old Male, Iliac Bone

A 17-year-old male reported a 2-year history of left hip pain and restricted mobility, initially suspected to be osteosarcoma. A palpable mass was noted on examination. Radiography revealed an osteolytic lesion in the left iliac bone, and CT confirmed a heterogeneous soft tissue mass involving the iliac bone and sacrum, with pulmonary metastases detected on chest CT. An incisional biopsy demonstrated a small round blue cell tumor. IHC revealed strong CD99 (>90%) and FLI-1 (>90%) positivity, with weak-to-moderate nuclear TLE positivity in 50% of cells, and negative SATB2, SMA, Desmin, CK, and S100, excluding osteosarcoma and other sarcomas, confirming classical Ewing sarcoma.

Extraskeletal Ewing's Sarcoma Cases

Case 9: 18-Year-Old Female, Kidney

An 18-year-old female presented with flank pain and a right renal mass. Ultrasonography revealed a 10 × 5 cm mass with renal vein thrombosis, and CT confirmed a heterogeneous lesion (7.7 × 6.2 cm) with pulmonary and pleural metastases. An ultrasonography-guided biopsy showed a small round blue cell tumor. IHC demonstrated strong CD99 (>90%) and FLI-1 (>95%) positivity, with negative Tdt and MyoD1, confirming extraskeletal Ewing sarcoma.

Case 10: 18-Year-Old Female, Nasal Cavity

An 18-year-old female presented with a right nasal mass causing obstruction and orbital symptoms. CT revealed a soft tissue mass eroding the lamina papyracea, extending into the right orbit, and displacing the medial rectus. Histopathology confirmed a small round blue cell tumor .IHC showed CD99 and weak-to-moderate FLI-1 (90%) positivity, with negative Tdt, CD45, and MyoD1, establishing extraskeletal Ewing sarcoma.

Case 11: 70-Year-Old Female, Heel

A 70-year-old female presented with a 2 × 2 cm hard swelling on the left heel, initially misdiagnosed as a pyogenic granuloma. Ultrasonography suggested a keratinous cyst, but excisional biopsy revealed a small round blue cell tumor. IHC showed CD99 and FLI-1 positivity, with SMA and CD34 positivity in vessels only, and negative EMA, HMB45, CD3, CD20, CK, CD68, and Melan A, confirming extraskeletal Ewing sarcoma.

Case 12: 7-Year-Old Male, Lung

A 7-year-old male presented with chest pain and pleural effusion. CT revealed a heterogeneous lung mass with metastases. Biopsy histopathology

showed a small round blue cell tumor with uniform morphology. IHC confirmed CD99 and FLI-1 positivity, with negative CD45 and MyoD1, establishing extraskeletal Ewing sarcoma.

Case 13: 50-Year-Old Male, Lung

A 50-year-old male presented with a lung mass and pain. CT revealed a heterogeneous mass with pleural involvement. Histopathology showed a small round blue cell tumor. IHC demonstrated CD99 and FLI-1 positivity, with negative Desmin and CD45, confirming extraskeletal Ewing sarcoma.

Case 14: 40-Year-Old Male, Lung

A 40-year-old male presented with chest pain and a right lung mass. CT-guided biopsy revealed a small round blue cell tumor. IHC showed strong FLI-1 (>90%) and moderate ERG (60%) positivity, with negative HMB45 and CD31, confirming extraskeletal Ewing sarcoma.

Table 1: Classical Ewing's Sarcoma Cases (n=8)

Case No	Age/Sex	Site	Clinical Presentation	Imaging Findings	Histopathology	IHC Results
1	26/M	Costophrenic mass	Prior excision, no dyspnea	CECT: Heterogeneous mass (8.1x7.1x3.1 cm)	Small round blue cell tumor	CD99: >80%; FLI-1: >90%; MyoD1, NSE, CD34, OCT3/4, PLAP, PANCK: Negative
2	7/M	Ulna	Pain, swelling	X-ray: Osteolytic lesion	Small round blue cell tumor	CD99, FLI-1: Positive
3	15/M	Maxilla	Swelling	CT: Lytic lesion with soft tissue extension	Small round blue cell tumor	CD99, FLI-1: Positive
4	22/M	Femur	Pain, limited movement	X-ray: Osteolytic lesion; MRI: Soft tissue mass	Small round blue cell tumor	CD99, FLI-1: Positive
5	30/F	Rib	Pain, mass	CT: Osteolytic lesion	Small round blue cell tumor	CD99, FLI-1: Positive
6	40/M	Pelvis	Pain, swelling	CT: Lytic mass	Small round blue cell tumor	CD99, FLI-1: Positive
7	13/M	Clavicle	Swelling x 5 months	X-ray: Osteolytic lesion; MRI: Lytic mass (3x4.3x4 cm)	Small round blue cell tumor	CD99: >90% membranous; FLI-1: >90% nuclear; Tdt: Occasional; CD45, CD1a, MyoD1: Negative
8	17/M	Iliac bone	Hip pain x 2 years	X-ray: Osteolytic lesion; CT: Heterogeneous mass, lung metastases	Small round blue cell tumor	CD99: >90%; FLI-1: >90%; TLE: 50% weak-moderate; SATB2, SMA, Desmin, CK, S100: Negative

Table 2: Extraskeletal Ewing's Sarcoma Cases (n=6)

Case No	Age/ Sex	Site	Clinical Presentation	Imaging Findings	Histopathology	IHC Results
9	18/F	Kidney	Renal mass	USG: 10x5 cm mass; CT: 7.7x6.2 cm lesion, pulmonary/pleural metastases	Small round blue cell tumor	CD99: >90%; FLI-1: >95%; Tdt, MyoD1: Negative
10	18/F	Nasal cavity	Nasal mass, orbital extension	CT: Mass eroding lamina papyracea	Small round blue cell tumor	CD99: Positive; FLI-1: Weak-moderate 90%; Tdt, CD45, MyoD1: Negative
11	70/F	Heel	2x2 cm hard swelling	USG: Keratinous cyst	Small round blue cell tumor	CD99, FLI-1: Positive; SMA, CD34: Vessel-positive; EMA, HMB45, CD3, CD20, CK, CD68, Melan A: Negative
12	7/M	Lung	Pain, pleural effusion	CT: Mass with metastases	Small round blue cell tumor	CD99, FLI-1: Positive
13	50/M	Lung	Pain, mass	CT: Heterogeneous mass	Small round blue cell tumor	CD99, FLI-1: Positive
14	40/M	Lung	Lung mass	CT: Heterogeneous mass	Small round blue cell tumor	FLI-1: >90%; ERG: 60%; HMB45, CD31: Negative

Table 3: Comparison of Classical vs. Extraskeletal Ewing Sarcoma

Feature	Classical Ewing Sarcoma	Extraskeletal Ewing Sarcoma
Site	Bones (clavicle, ulna, iliac bone, maxilla, pelvis)	Soft tissues (lung, kidney, nasal cavity, heel)
Age Distribution	Predominantly pediatric (7–40 years in this series)	Bimodal (<5 or >35 years; 7–70 years in this series) [1,3]
Incidence	3 per 100,000 [2]	0.4 per million [1]
Clinical Presentation	Pain, swelling, osteolytic lesions [2,5]	Mass, atypical symptoms (e.g., nasal obstruction, heel swelling) [1]
Imaging	Osteolytic lesions, "onion-peel" effect, Codman's triangle [2]	Heterogeneous soft tissue masses [1]
Metastasis	Lungs (25% at diagnosis) [5]	Lungs, pleura [5,7]
Histopathology	Small round blue cell tumor, glycogen-rich [2,6]	Small round blue cell tumor, glycogen-rich [6]
IHC Markers	CD99, FLI-1 positive [4,6]	CD99, FLI-1 positive; occasional ERG [3,4]
Prognosis	Better with early intervention [7]	Poorer due to delayed diagnosis [1,7]

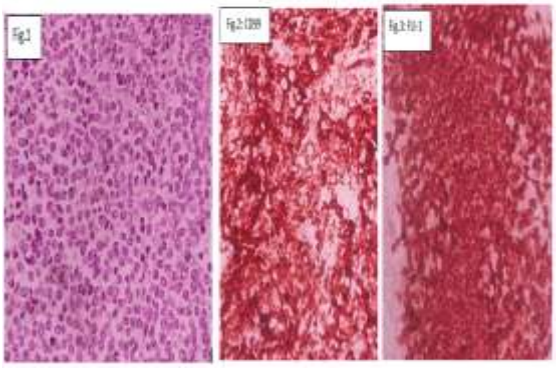

Figure 1-3: Cases 1-6 and 9-13: small round blue cell tumor morphology with CD 99 and FLI-1 positivity

Figure 4: Case 7: Tdt positivity in occasional cells

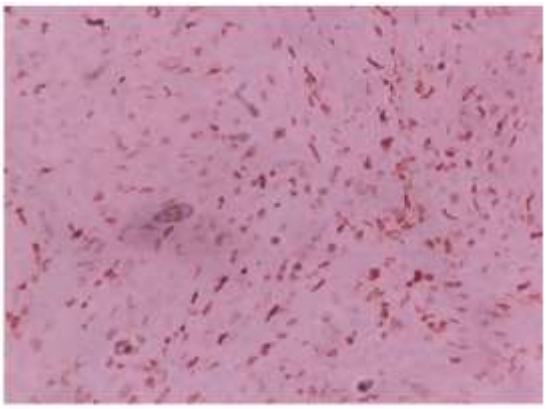

Figure 5: Case 8: TLE -weak to moderate positivity in tumor cells

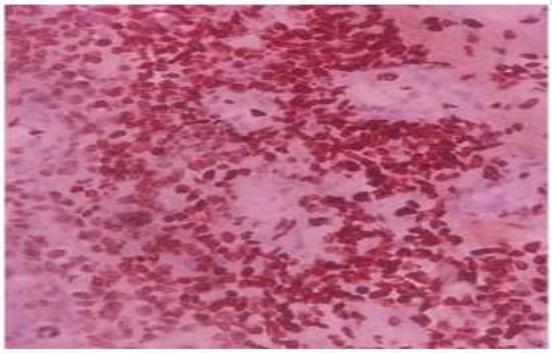

Figure 6: Case 14- ERG positivity in 60% of tumor cell

DISCUSSION

Extraskeletal Ewing sarcoma (EES) is a rare malignant tumor of mesenchymal origin, typically presenting in children and young adults, and poses significant diagnostic and therapeutic challenges due to its histological resemblance to other small round cell tumors. In our study comprising 14 histologically confirmed cases, the age range spanned from 8 to 48 years, with a mean age of 20.5 years, aligning with the epidemiological pattern noted by Kennedy *et al.*, who reported a peak incidence in adolescents and young adults, particularly with paraspinal and pelvic involvement [10]. Males predominated, accounting for 10 out of 14 cases (71.4%), which is consistent with the male-to-female ratio seen in prior case series.[10]

Clinically, pain was the most frequent symptom, noted in 13 patients (92.8%), followed by swelling or a palpable mass in 9 patients (64.3%). Pulmonary metastasis was observed in 4 patients (28.6%) at the time of presentation. Grier *et al.*, in their seminal study involving 478 patients, similarly emphasized that nearly 25% of patients had metastatic disease at diagnosis, often to the lungs or bones, which correlates with our findings.[11]

Radiologically, soft tissue masses with ill-defined margins were noted in all cases, with MRI being the most helpful in delineating the extent. Wang *et al.* conducted a retrospective analysis of pediatric mediastinal Ewing sarcoma cases and demonstrated characteristic heterogeneous signal intensities and necrotic areas on T2-weighted imaging, similar to features observed in our paraspinal and retroperitoneal cases.[16] The addition of ifosfamide

and etoposide has been associated with improved 5-year event-free survival, rising from 54% to 69% [11]. Histopathologically, all tumors displayed classic features of Ewing sarcoma: small, round, blue cells with high nuclear-to-cytoplasmic ratio. Immunohistochemically, CD99 showed strong membranous positivity in all 14 cases (100%). Pasricha *et al.* from an Indian tertiary center highlighted that combining NKX2.2 and CD99 had 96% diagnostic concordance with EWSR1 FISH results, suggesting this dual IHC panel may sufficiently obviate the need for molecular testing in most cases.[12]

Cytokeratin expression was seen in 2 of our cases (14.3%), which raised initial suspicion of carcinoma. However, further immunoprofiling confirmed the diagnosis of Extraskeletal Ewing's sarcoma. This observation resonates with Rooper *et al.*, who emphasized that adamantinoma-like variants of Ewing sarcoma, particularly in head and neck sites, may mimic poorly differentiated carcinomas due to epithelial marker expression [13].

One case in our study showed neuroectodermal differentiation with rosette formation. Similar histological heterogeneity was documented by Çomunoğlu *et al.*, who described a case with extensive well-differentiated neuroblastomatous features, complicating the diagnosis without immunohistochemistry and molecular confirmation.[14]

Interestingly, one case of prenatal EES reported by Picard *et al.* identified a novel in-frame TAF15–ETV4 fusion, expanding the molecular landscape of this tumor family.[15] Though not seen in our study, this reinforces the growing role of advanced genomic studies in identifying non-canonical translocations in morphologically ambiguous tumors.

ERG, a transcription factor from the ETS family, has recently gained attention as a useful diagnostic marker. In our study, ERG IHC was positive in 6 out of 14 cases (42.8%), especially in those suspected to harbor EWSR1–ERG fusion. Yoshida *et al.* had demonstrated that ERG expression strongly correlated with EWSR1–ERG fusions, with high specificity.[19] Machado *et al.* also noted that ERG expression may supplement CD99 and NKX2.2 in diagnostically difficult cases.[20]

Further supporting its diagnostic relevance, Huang *et al.* demonstrated that ERG is useful in differentiating Ewing sarcoma from other small round blue cell tumors, with high sensitivity and specificity.[21] In our study, ERG was particularly valuable in cases where CD99 staining was strong but nonspecific. In contrast, Lee *et al.* showed that ERG positivity, in conjunction with EWSR1–ERG fusion, predicted a favorable prognosis, possibly suggesting a unique molecular subset within the Ewing sarcoma spectrum.[22]

While the diagnostic role of TLE1 is well-established in synovial sarcomas, one of our cases displayed focal positivity, necessitating exclusion of this differential. Terry *et al.* emphasized the use of TLE1 as a reliable marker for synovial sarcoma; however, its occasional expression in Ewing sarcoma underlines the need for molecular correlation.[18]

Our findings validate the combined use of CD99, ERG in diagnosing Ewing sarcoma, particularly in resource-limited settings where molecular testing may not be universally accessible. Additionally, atypical IHC expressions such as cytokeratin and TLE1 require cautious interpretation in the light of clinical, radiological, and morphologic correlation. Molecular studies, though confirmatory, may not be mandatory in the presence of a characteristic immunophenotype.

CONCLUSION

This case series of 14 patients with Ewing's sarcoma, diagnosed between January 2023 and May 2024, illuminates the diverse clinical, radiographic, histopathologic, and immunohistochemical spectrum of this rare malignancy, encompassing eight classical and six extraskeletal cases across ages 7 to 70 years.[1,3] The inclusion of atypical sites, such as the heel and nasal cavity, highlights significant diagnostic challenges, particularly in adults where the disease is less expected.[1,13] All cases displayed small round blue cell morphology and consistent CD99 and FLI-1 positivity, underscoring IHC's critical role in distinguishing Ewing's sarcoma from mimics like lymphoma and rhabdomyosarcoma.[4,6] The 25% pulmonary metastatic rate at diagnosis reflects the disease's aggressive nature, emphasizing the need for early diagnosis to improve outcomes.[7] The study's novelty lies in its broad age range and rare extraskeletal presentations, which expand the clinical understanding of Ewing's sarcoma beyond its pediatric predominance.[1,3] The comprehensive IHC panel, incorporating NKX2.2 and ERG, resolved complex differentials, aligning with Pasricha *et al.*'s findings.[12] This approach, combined with clinical evaluation, advanced imaging, and histopathology, exemplifies the multidisciplinary strategy advocated by Gaspar *et al.*[7] The geriatric heel case and nasal cavity presentation with orbital extension highlight the necessity of considering Ewing's sarcoma across all ages and sites, as supported by Kennedy *et al.* and Rooper *et al.*[10,13]. Future research should refine diagnostic protocols with molecular tools, such as EWSR1 rearrangements, and explore prognostic factors for atypical sites to enhance early detection and therapeutic outcomes.[3,12] This series advances the recognition and management of Ewing sarcoma, advocating for standardized diagnostic approaches to address its diagnostic and therapeutic challenges.

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