

Beyond the Usual Suspects – An Atypical Bone Marrow Presentation of Ewing Sarcoma: A Case Report.

Hari Priya Raghvan¹, Wee Shiang Yui¹, Caroline Ho Siew Ling¹, Sharllina Prasad¹, Ehram Jamian¹, Indhira Subbiah¹, Noraida Khalid¹.

ABSTRACT

Ewing sarcoma (ES) is a malignancy that occurs in childhood and young adolescent and has a predilection for certain site such as femur. This case is an atypical presentation of ES diagnosed through bone marrow examination in a young adult. We present a case of Ewing Sarcoma with bone marrow involvement in a young male who initially had hypercalcemia with back pain and was initially thought to have Plasma Cell Myeloma. This case highlights the diagnostic challenge posed by marrow-infiltrating ES when clinical and biochemical findings mimic Plasma Cell Myeloma. Awareness of this rare presentation is critical for early diagnosis and management.

Keywords

ewing's sarcoma; hypercalcemia; small round blue cell tumor

INTRODUCTION

Ewing's sarcoma (ES), previously known as the Ewing sarcoma family of tumors (ESFT) or primitive neuroectodermal tumor, is an aggressive and rare cancer initially identified in 1921. It usually arises in the diaphysis of long bones as a primary bone malignancy. Histologically, it is grouped as small round blue cell tumors and is most often associated with a specific chromosomal translocation—t(11;22).

ES primarily affects children and adolescents, frequently manifesting as a localized tumor in long bones or the pelvis. It often comes to clinical attention following symptoms such as

pain or pathological fractures. In some cases, metastases are present at diagnosis, though not always overt. Hypercalcemia as a presenting feature is extremely uncommon. These tumors share overlapping morphological features, and immunohistochemistry plays a crucial role in their differential diagnosis. Standard treatment typically involves systemic chemotherapy combined with local control through surgery and/or radiotherapy.

Case report

Our case is a 22-years-old male who presented with back pain and bilateral lower limb numbness for 1 month duration. On examination, there was no palpable lymphadenopathy or hepatosplenomegaly. No other mass detected. Full blood count revealed a haemoglobin of 88g/L, white blood cells (WBC) of $11.1 \times 10^9/L$ with mild neutrophilia of $8.5 \times 10^9/L$ and platelet of $220 \times 10^9/L$. Serum calcium was noted to be slightly raised (2.93 mmol/L). Alkaline phosphatase (ALP) was increased with 409 U/L (normal range: 40-150 U/L). Serum albumin was low with 28g/L and total protein was 89g/L. Serum LDH was elevated with 768 U/L (normal range: 125-220 U/L). Renal profile was within normal range. Viral screenings were non-reactive. Full blood picture was reported as presence of few short rouleaux but no blasts/abnormal lymphoplasmacytoid cells seen. Serum and urine electrophoresis and serum free

1. Hospital Sultanah Aminah, Johor Bahru, Johor, Ministry of Health, Malaysia.

Correspondence

Hari Priya Raghvan, Department of Pathology, Hospital Sultanah Aminah, Johor Bahru, Johor, Ministry of Health, Malaysia. Email : priya_hari88@yahoo.com

light chain ratio were sent, but no paraproteins were detected. Serum parathyroid hormone (PTH) was low with <0.58 pmol/L (normal range: 1.58-6.03 pmol/L).

A magnetic resonance imaging were done which showed multiple lytic bony lesions and acetabular fracture (Figure 1). A bone marrow examination was undertaken. Bone marrow aspirate showed abnormal mononuclear cells which are adhesive, and some are scattered singly. They are medium in size, exhibiting moderate to scanty bluish cytoplasm and with clumped chromatin pattern (Figure 2). Trephine biopsy revealed infiltration by non-haematopoietic cells in diffuse sheets. Some of them are small in size with indistinct nuclear membranes, high nuclear to cytoplasmic ratio, clumped chromatin pattern and inconspicuous nucleoli. Some of the cells are medium to large in size with clear cytoplasm, more dispersed chromatin pattern and inconspicuous nucleoli. They are positive for CD99 (strong), NKX2.2, and FLI-1 with Ki-67 proliferative index of around 50% (Figure 3). All other immature markers, B-cells, T-cells, and plasma cells markers were negative, thus, highly suggestive of Ewing Sarcoma.

Ethical clearance

Ethical approval is not required for reporting individual cases in our institution. Informed consent was obtained from the patient.

DISCUSSION

Ewing sarcoma (ES) is classically a malignancy of children and young adults that ranks the second among the primary bone tumours in childhood/adolescent age group¹. Over 80% of them occur in the 1st–2nd decades of life, and the femur, pelvis, and chest wall are common sites. Constitutional symptoms (fever, weight loss) may occur in advanced disease, but early ES is often mistaken for benign conditions

Ewing sarcomas' presentation can differ according to the site of involvement but commonly includes local symptoms and fever. Up to 20–30% of ES arise outside bone as extraskeletal Ewing sarcoma, often in soft tissues of the trunk, extremities, or head and neck. ES has been reported in unusual sites such as pelvis² and in older patients beyond adolescence. Our 22-year-old patient lies at the upper end of the typical age range and had multifocal skeletal involvement, features more often seen in disseminated ES or in adults. The occurrence of multiple bony lesions and even visceral

metastases³ has been documented in ES, underscoring that widespread disease can be the initial presentation in rare cases as seen in our case.

Hypercalcemia is an exceedingly rare manifestation of ES⁴. Hypercalcemia of malignancy is common in adult carcinomas (e.g. lung, breast). In our case, PTH was suppressed, indicating a PTH-independent mechanism⁵. 3 main causes of hypercalcemia in malignancy have been described; first is humoral factors released in a paracrine or endocrine manner. Second, in patients with significant tumor burden that has spread to bone, the local tumor effects can directly promote bone breakdown and calcium release (local osteolysis). Less frequently, absorptive hypercalcemia arises from the tumor's excessive activation of vitamin D. In our opinion, the most likely cause in our case is massive osteolysis from bone metastases, which releases calcium into the circulation⁶. Indeed, published ES cases with hypercalcemia have involved multifocal skeletal and marrow disease. Recent ES case series emphasize that ES patients presenting with hypercalcemia or a hypercalcemic crisis almost invariably have extensive disseminated disease and a very guarded prognosis⁴.

The presentation of a young adult with multiple lytic bone lesions, hypercalcemia, anemia and a reversed albumin–globulin ratio raises an immediate concern for multiple myeloma or other hematologic malignancies. In fact, classical myeloma often causes hypercalcemia, bone pain, renal failure, anemia and reversal of the albumin:globulin ratio. Our patient's normal serum protein electrophoresis essentially excluded a monoclonal gammopathy, highlighting a diagnostic pitfall. Similarly, marrow infiltration by non-hematopoietic cells points towards a metastatic small round blue cells tumor. In adolescents and young adults, differentials for osteolytic lesions include ES, osteosarcoma, lymphoma, histiocytosis, plasma cell myelomas, and rare metastatic carcinomas⁷. Bone marrow metastasis in ES has a poor prognosis⁸. Although the findings from the bone marrow examination in our case, are highly suggestive of ES, we believe that a biopsy of the soft tissue lesion remains essential. A definitive diagnosis of Ewing sarcoma should ideally be established from the primary soft tissue or bone lesion rather than from marrow involvement alone with characteristic histology and immunohistochemistry, especially when molecular testing is unavailable.

Histologically, ES is a “small round blue cell tumor” that can mimic lymphoma or other PNETs. Typical findings include sheets of small uniform cells with scant cytoplasm and round nuclei. Immunohistochemically, nearly all ES cells express membranous CD99 and often FLI1⁹ and many express NKX2.2¹⁰. However, CD99 is not entirely specific; other sarcomas and lymphomas may also stain¹⁰. Thus expert pathologic review is critical. Current guidelines note that definitive diagnosis should be confirmed by immunohistochemistry and molecular pathology, since the classic EWSR1-FLI1 fusion (from t(11;22))¹¹ is present in ~85% of ES tumors. If molecular testing (FISH or RT-PCR for EWSR1 rearrangement) is not performed, a combination of IHC markers and the clinical picture can establish the diagnosis. In our case, the bone marrow biopsy showed small round cells that were positive for ES-specific markers and negative for lymphoma markers, clinching the diagnosis despite lack of genetic confirmation (not available in our case). This emphasizes the value of biopsy with a broad IHC panel when ES is suspected, especially in adults with lytic lesions and marrow involvement.

Metastatic ES carries a poor prognosis and requires aggressive multimodal therapy¹². The presence of hypercalcemia in our patient signals a high tumor burden and likely advanced disease. Standard treatment would involve multiagent chemotherapy (doxorubicin, cyclophosphamide, vincristine, etoposide, ifosfamide, and dactinomycin) combined with local control measures (surgery and/or radiotherapy) for accessible lesions¹².

In summary, this case illustrates both classic and unusual aspects of ES. While ES typically affects adolescents

with a solitary bone tumor, clinicians must recognize that adults can present with multifocal bone disease and paraneoplastic syndromes like hypercalcemia. The reversed albumin/globulin ratio and bone lesions initially mimicked plasma cell myeloma, underscoring the need to confirm the cause of hypercalcemia. Ultimately, biopsy with IHC established the ES diagnosis. Our report reinforces that rare features (extraskelatal spread and hypercalcemia) of ES are associated with disseminated disease and demand prompt, tailored management.

Conflict of Interest

The authors declare no conflict of interest.

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Authors's contribution

Data gathering and idea owner of this study: Hari Priya Raghvan

Study design: Hari Priya Raghvan, Wee Shiang Yui, Caroline Ho Siew Ling

Data gathering: Hari Priya Raghvan, Wee Shiang Yui, Sharllina Prasad, Noraida Khalid

Writing and submitting manuscript: Hari Priya Raghvan, Wee Shiang Yui, Caroline Ho Siew Ling

Editing and approval of final draft: Sharllina Prasad, Ehram Jamian, Indhira Subbiah, Noraida Khalid

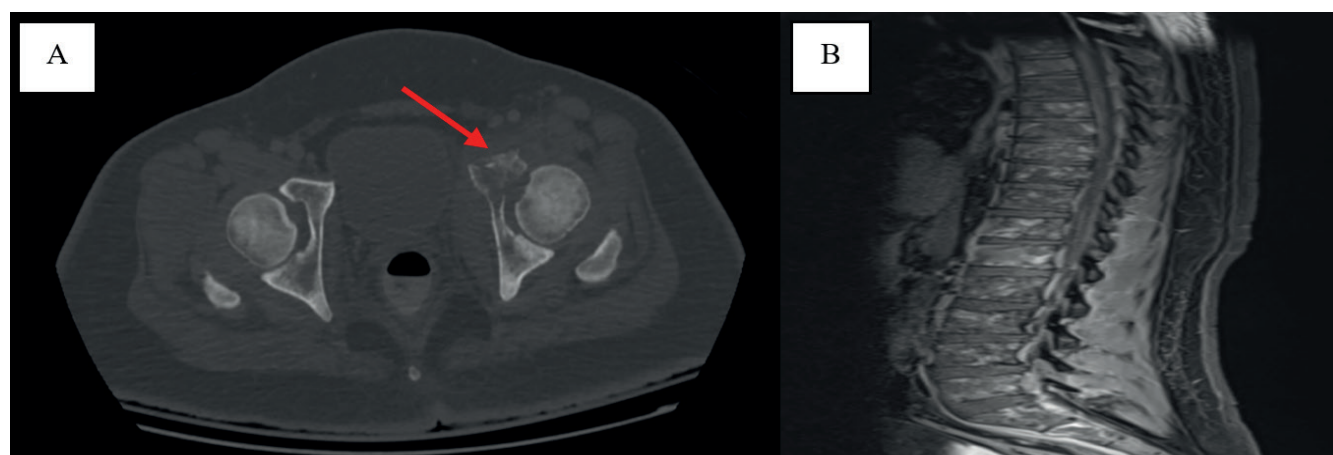


Figure 1: A) Computed tomography axial view bone window showing left anterior acetabular wall pathological fracture (red arrow), **B)** Magnetic resonance imaging spine post contrast in sagittal view showing multilevel enhancing vertebral lesions.

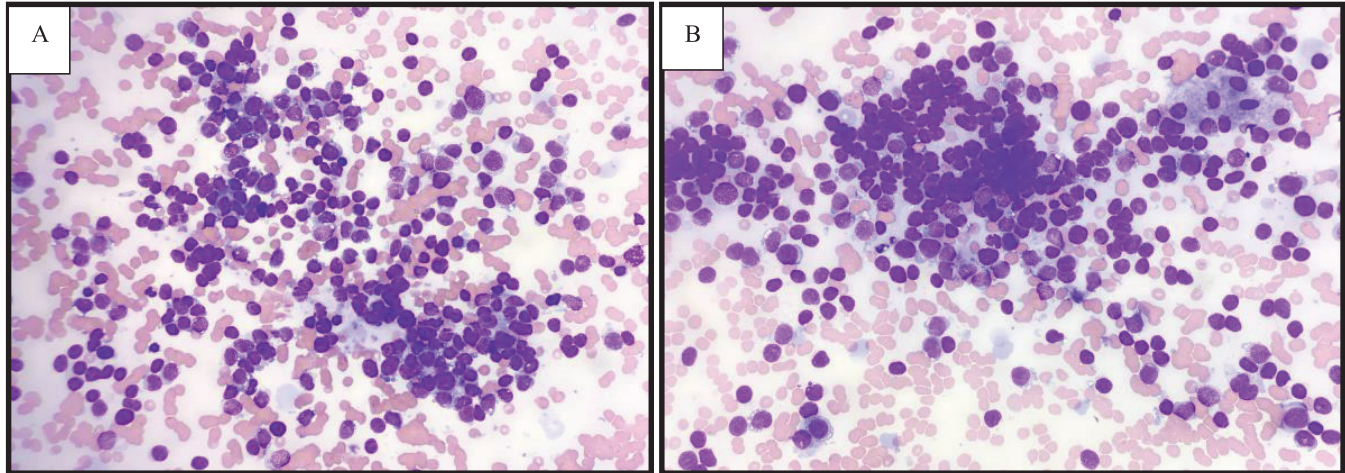


Figure 2: Bone marrow aspirate. **A&B)** Presence of non-haematopoietic cell infiltration which are cohesive and some are singly distributed (MGG, X200).

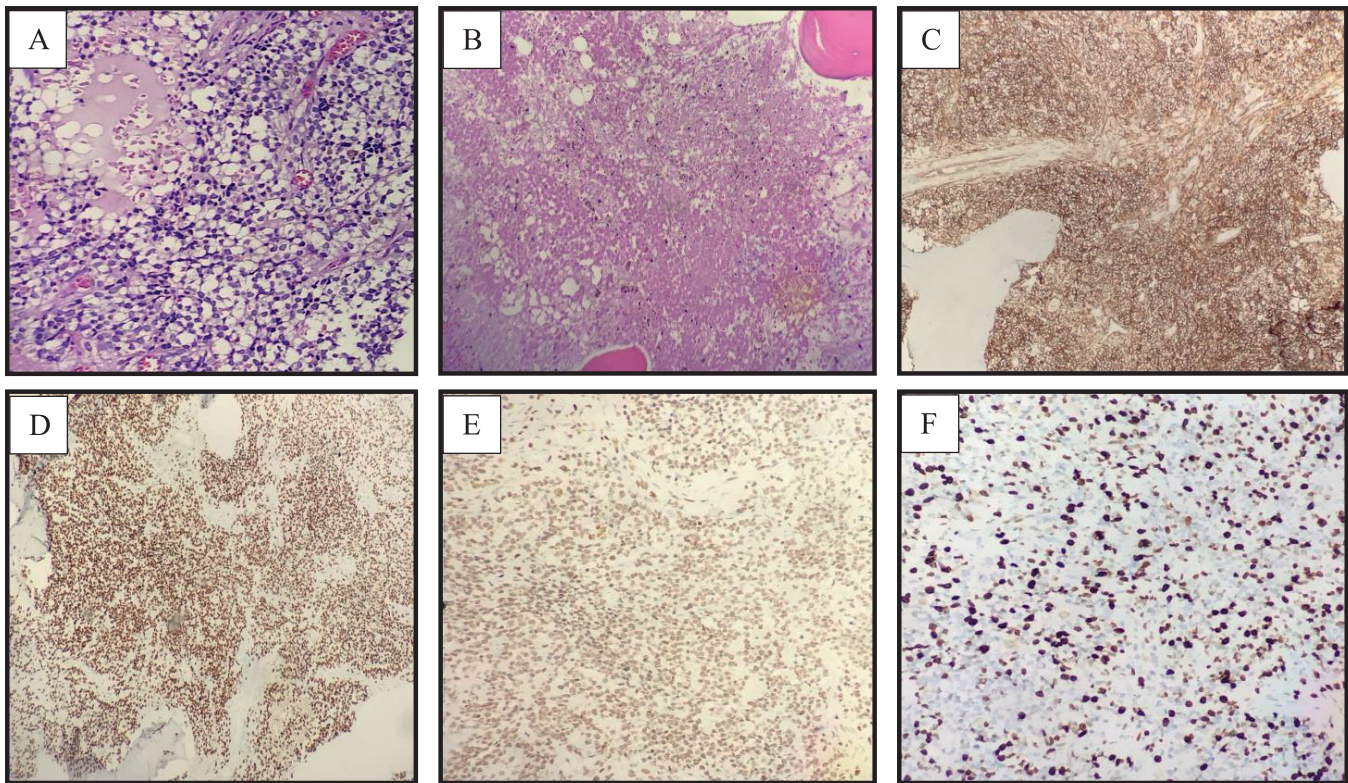


Figure 3: Trephine biopsy. **A)** Infiltration by small round blue cell tumors (H&E, X200) **B)** Areas of necrosis (H&E, X200). The cells are positive for **C)** CD99 (strong, diffuse and membranous staining)(X200), **D)** NKX2.2 (X200), **E)** FLI1 (X200), and **F)** Ki-67 proliferative index of around 50% (X200).

REFERENCES

1. Narayanan, G., Kamala, L. H., Nair, S. G., Purushothaman, P. N., Kumar, A., & Kattoor, J. (2024). Ewing's sarcoma in adolescents and adults–10-year experience from a tertiary cancer center in India. *Journal of Cancer Research and Therapeutics*, **20**(1): 79-84.
2. Jones, L. B., & Barr, J. S. (2016). Bone sarcomas: an update of the recent literature. *Current Orthopaedic Practice*, **27**(6):582-586.
3. Guduguntla, B. A., Shi, J., & Kwon, R. S. (2022). Ewing sarcoma: Rare metastasis to the pancreas. *ACG Case Reports Journal*, **9**(12): e00930.
4. Haldhar, A., Lohar, R., Kumbhar, S. S., Kant, R., Dhar, M., HALDHAR, A., & KUMBHAR, S. (2023). Hypercalcemic Crisis: A Rare Presentation of Ewing's Sarcoma. *Cureus*, **15**(12): 1-5.
5. Vakiti, A., Anastasopoulou, C., & Mewawalla, P. (2018). Malignancy-related hypercalcemia.
6. Rosner, M. H., & Dalkin, A. C. (2012). Onco-nephrology: the pathophysiology and treatment of malignancy-associated hypercalcemia. *Clinical Journal of the American Society of Nephrology*, **7**(10): 1722-1729.
7. Subramanian S, Viswanathan VK. Lytic Bone Lesions. [Updated 2024 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539837/>
8. Park, K., Kim, H., Koh, K. N., Im, H. J., Cho, Y. U., Jang, S., Seo, E. J., & Park, C. J. (2021). Bone Marrow Findings in Patients With Ewing Sarcoma/Primitive Neuroectodermal Tumor. *Annals of laboratory medicine*, **41**(5): 499–501. <https://doi.org/10.3343/alm.2021.41.5.499>
9. Lee, A. F., Hayes, M. M., LeBrun, D., Espinosa, I., Nielsen, G. P., Rosenberg, A. E., & Lee, C. H. (2011). FLI-1 distinguishes Ewing sarcoma from small cell osteosarcoma and mesenchymal chondrosarcoma. *Applied Immunohistochemistry & Molecular Morphology*, **19**(3): 233-238.
10. Ullah, A., Sinkler, M. A., Zarate, L. V., Clavijo, A., & White, J. (2021). Ewing sarcoma and Ewing-like sarcoma and the role of Nkx2. 2 immunoreactivity. *Cureus*, **13**(8): 1-5.
11. Singh K, Raychaudhuri S, Chauhan V, Bajaj A, Menia R. Unusual Presentation of Peripheral Primitive Neuroectodermal Tumor: A Rare Case Report.
12. Mata Fernández, C., Sebio, A., Orcajo Rincón, J., Martín Broto, J., Martín Benlloch, A., Marcilla Plaza, D., ... & Valverde Morales, C. (2025). Clinical practice guidelines for the treatment of Ewing sarcoma (Spanish Sarcoma Research Group-GEIS). *Clinical and Translational Oncology*, **27**(3): 824-836.