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Case Report

Case Report: "Small Round Blue Cells in Pediatric Oncology": A Great Mimicker!

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Abstract

Small round blue cell tumors (SRBCTs) include diverse group of aggressive pediatric oncology that pose significant diagnostic challenges because of their overlapping histological features. These includes neuroblastoma (NB), rhabdomyosarcoma, non-Hodgkin's lymphoma, Ewing's sarcoma and the closely related primitive neuroectodermal tumour (PNET) and the blastemal component of Wilms tumour. The tumours have similar appearance by light microscopy and partial overlap in immunohistochemical (IHC) profiles. Accurate diagnosis of this condition requires a comprehensive evaluation involving clinical presentation, imaging, histopathology and immunohistochemistry. Herein, we report a rare case of a 3-year-old male presenting with right lower limb pain and a retroperitoneal mass with bone marrow involvement. This case highlights the diagnostic complexity of SRBCTs and the importance of a meticulous diagnostic approach in pediatric oncology. Timely diagnosis and intervention are crucial, guided by a high clinical suspicion and characteristic histopathological findings. Advances in treatment modalities offer hope for improved outcomes in this challenging malignancy.

Keywords: Small Round Blue Cell; Neuroblastoma; Childhood Malignancy; Pediatric Oncology

Introduction

SRBCTs co looooovers a diverse group of undifferentiated or poorly differentiated malignancies that predominantly affect the children and adolescents. These tumors are characterized histologically by small, round blue cells with high nuclear-to-cytoplasmic ratio, scant cytoplasm and hyperchromatic nuclei. These include neuroblastoma, Ewing sarcoma/PNET, rhabdomyosarcoma, lymphoblastic lymphoma and others. Accurate differentiation is very important, as each subtype has variable clinical symptoms, prognosis and treatment strategies [1,2].

The diagnostic challenge arises because of overlapping morphological features, particularly in bone marrow aspirates, where SRBCTs may mimic hematological malignancies such as acute leukemia or lymphoma [3]. In many cases, patients may initially present with vague symptoms such as bone pain, fever, weight loss or fatigue [4]. Imaging studies such as PET-CT (Positron Emission Tomography/Computed Tomography) MRI and MIBG scans play an important role in identifying the extent of disease.

SRBCTs commonly infiltrate the bone marrow, where they maybe mistaken for leukemia or lymphoma, further complicating the diagnosis. Bone marrow involvement is particularly common in high-risk tumors and it often signifies the advanced disease. Immunohistochemistry plays a very vital role in distinguishing between these malignancies and molecular via MYCN amplification, ALK mutations, or EWSR1 rearrangement are often required for confirmation. Most small round blue cells in BM pediatric pathology are attributable to leukaemias and lymphomas.

Case Report

A 03-year-old male presented with pain right lower limb of one month duration associated with low grade fever. It was intermittent in nature, non-radiating, associated with limping gait, which aggravated on exertion and relieved on medication. Initial clinical evaluation revealed pallor, hepatomegaly and tenderness over right hip joint. An initial diagnosis of ostemomyelitis was rendered and intravenous antibiotics were given. Ultra sonography abdomen revealed multiple paravertebral lesions in retroperitoneum and mediastinum and a mass lesion in right lobe of liver measuring 8.1 x 5.8 x 10cm. Bone marrow aspirate revealed a cellular bone marrow aspirate showing small round blue cells forming rosettes at places. These cells show high N:C ratio, scant cytoplasm, round to oval nuclei with stippled chromatin and inconspicuous nucleoli. Bone marrow biopsy confirmed diffuse replacement by similar tumor cells, with focal rosette formation and brisk mitotic activity (Figure 1). Immunohistochemistry (IHC) showed tumor cells that were positive for synaptophysin, chromogranin and CD56 and are negative for Pan CK, Desmin, Tdt, WT1 and CD99 (Figure 2). The combined histopathological and IHC findings were consistent with small round blue cell tumor highly suggestive of neuroblastoma. Cervical lymph node biopsy from the same patient also shows metastatic deposits composed of similar tumor morphology, which was positive for chromogranin, CD99, CD56, Vimentin, ALK-1 with Ki67 proliferating index of 90% and negative for Pan CK, GFAP, SALL4, WT-1, p40, CD3, CD20, S-100.

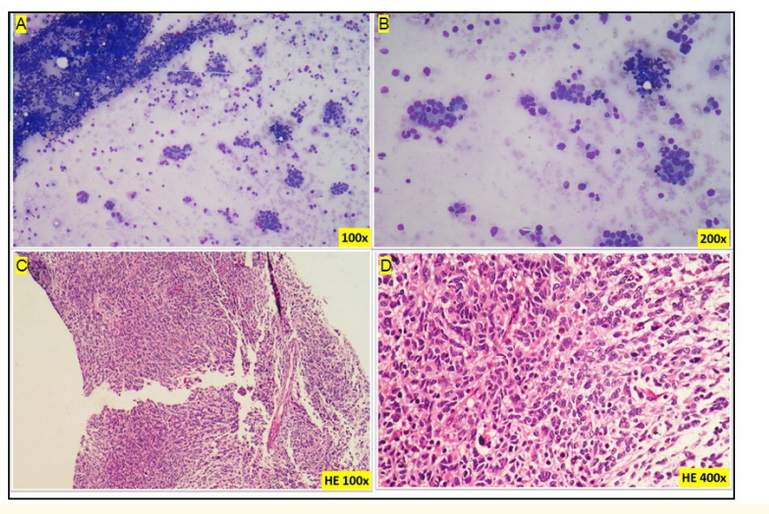

Figure 1: A,B Cellular bone marrow aspirate showing small round blue cells forming rosettes places. These cells show high N:C ratio, scant cytoplasm, round to oval nuclei with stippled chromatin and inconspicuous nucleoli. C,D: Bone marrow biopsy showing tumor cells in sheets as well as clusters forming rosette like morphology at places. Brisk mitosis also noted.

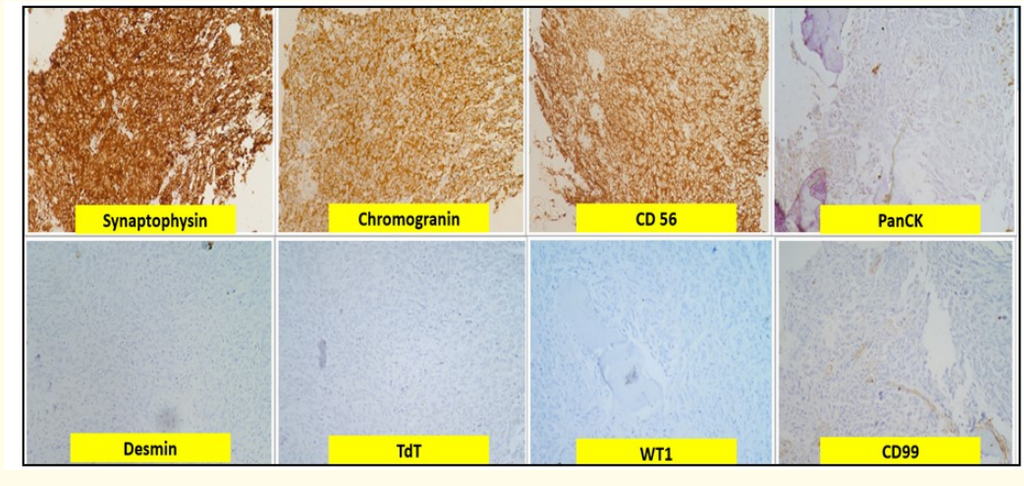

Figure 2: Immunohistochemistry showing tumor cells positive for synaptophysin, chromogranin & CD56 and are negative for PanCK, Desmin, Tdt,WT1 and CD99.

Although molecular studies such as MYCN amplification, ALK mutation and FISH for EWSR1 were not done in this case, the diagnosis of neuroblastoma was confidently made based on clinical presentation, morphology and consistent IHC profile. This limitation is acknowledged and it highlights the reliance on traditional histopathological techniques in settings without access to molecular diagnostics. The patient was initiated on induction chemotherapy as per high-risk neuroblastoma protocol and follow-up was done with imaging.

Discussion

The diagnosis of SRBCTs is challenging due to their overlapping morphological features. Neuroblastoma, Ewing sarcoma, rhabdomyosarcoma and lymphoblastic lymphoma are some of the common entities within this category, and distinguishing between them is very crucial for guiding appropriate treatment. In this case, the presence of rosette formation in the bone marrow aspirate, combined with positive immunohistochemical markers such as synaptophysin, chromogranin and CD56, favours a diagnosis of neuroblastoma.

Neuroblastoma commonly presents with Homer-Wright rosettes, but this feature can also appear in other SRBCTs [1,5]. Ewing sarcoma, lacks rosette formation but it shows strong CD99 positivity and EWSR1 gene rearrangement, distinguishing it from neuroblastoma [6]. Rhabdomyosarcoma is another differential diagnosis which may mimic SRBCT morphology but it can also be confirmed by Desmin, Myogenin, and MyoD1 positivity, while lymphoblastic lymphoma usually exhibits TdT positivity and lymphoid marker expression, which were negative in this case [7]. Hence, Immunohistochemistry plays an important role in excluding these entities and confirming the neuroendocrine profile of the tumor (Figure 2).

Imaging studies, particularly PET/CT and MIBG scans, provides very crucial insight into the extent of disease in this case. MIBG scanning is highly specific for neuroblastoma, while PET/CT helps in assessing metabolically active lesions across various malignancies [8]. Although the patient imaging strongly suggested neuroblastoma, histopathological confirmation was necessary to exclude the mimics. Molecular studies like MYCN amplification and ALK mutation detection also plays a very important role in refining the diagnosis and guide risk stratification, they may not always be feasible [6]. Table 1 highlights important differential diagnosis to be considered in SRBCTs.

Differentials	Age	Common Sites	Cytomorphology	IHC	Genetic Features	Metastatic Pattern
Neuroblastoma	Infants to young children	Adrenal gland, abdomen, chest	SRBCs, Homer Wright rosettes	Synapto, Chromo, CD56	MYCN amplification,ALK mutation	Bone marrow, lymph nodes, lungs
Ewing Sarcoma	Children and adolescents	Bone, soft tissue	SRBCs in sheets	CD99, FLI1, NKX2.2	EWSR1 translocation	Lung, Bone, Soft tissue
Rhabdomyosarcoma	Infants to adolescents	Head and Neck, GI tract	SRBCs with rhabdomyoblastic differentiation	Desmin, Myogenin, MyoD1	FOXO1 translocation	Lungs, Lymph nodes, Bone
Lymphoblastic Lymphoma	Children and adolescents	Mediastinum, lymph nodes	Lymphoblasts with high N:C ratio, fine chromatin	TdT, CD3,CD79a	NOTCH1 mutations, TCR gene rearrangements	Bone marrow, CNS, lymph nodes

Table1: Differential diagnosis to be considered for small round blue cell tumors.

Accurate diagnosis of SRBCTs has therapeutic implications. In neuroblastoma, for risk stratification and treatment guidance, International Neuroblastoma Risk Group (INRG) classification system categorizes the patients based on their age, stage, MYCN amplification status and histological differentiation [8]. While low-risk and intermediate-risk neuroblastoma may respond well to surgery or limited chemotherapy, high-risk disease often requires an intensive chemotherapy, surgical resection, radiotherapy, autologous stem cell transplantation and immunotherapy [9]. Anti-GD2 immunotherapy with dinutuximab is now a standard part of post-consolidation treatment and it has shown to improve event-free survival [10]. Trials involving anti-GD2 chimeric antigen receptor (CAR) T-cell therapy and ALK inhibitors (e.g., lorlatinib) are still ongoing and show promise in relapsed or refractory cases [11,12]. In this case, confirming the diagnosis as neuroblastoma ensured that the patient was placed on an appropriate treatment regimen, avoiding unnecessary exposure to therapies intended for other malignancies. Despite these advances, challenges still remain in ensuring equitable access to molecular diagnostics and novel therapies across the different healthcare settings. This case highlights the importance of classical diagnostic tools when modern molecular techniques are inaccessible.

Conclusion

This case illustrates the diagnostic dilemma in small round blue cell tumors in pediatric oncology. The overlapping morphological and immunophenotypic profiles demand a thorough, methodical approach for accurate diagnosis. Multimodal evaluation including imaging, histopathology and immunohistochemistry is important to differentiate among entities such as neuroblastoma, Ewing sarcoma and rhabdomyosarcoma and further guide the effective management strategies. Even in the absence of molecular confirmation, the diagnosis of neuroblastoma can be made based on a systematic approach.

Advances in targeted therapy, immunotherapy and molecular profiling continue to improve the outcomes in patients with aggressive SRBCTs. Ongoing research into novel therapies such as anti-GD2 monoclonal antibodies and CAR T-cell strategies offers hope for a better prognostic outcomes and long-term survival for children with small round blue cell tumors. Additionally, molecular profiling is increasingly guiding personalized treatment strategies, improving survival outcomes by minimizing the treatment related toxicity. This case underscores the need for continued research and multidisciplinary collaboration to refine diagnostic strategies and expand treatment options for SRBCTs.

Bibliography

1. Irwin MS and Park JR. "Neuroblastoma: paradigm for precision medicine". *Pediatric Clinics of North America* 67.5 (2000): 965-981.

2. Smith V and Foster J. "High-risk neuroblastoma treatment review". *Children (Basel)* 5.9 (2018): 114.

3. Kaatsch P. "Epidemiology of childhood cancer". *Cancer Treatment Reviews* 41.3 (2005): 192-202.

4. Modrell V., *et al.* "Differential diagnosis of small round blue cell tumors: an immunohistochemical approach". *Archives of Pathology and Laboratory Medicine* 132.3 (2008): 368-380.

5. Olsen RJ., *et al.* "An update on the differential diagnosis of SRBCTs in children". *The American Journal of Surgical Pathology* 44.6 (2020): 781-798.

6. DuBois SG., *et al.* "Metastatic sites in stage IV neuroblastoma correlate with age, tumor biology, and survival". *Journal of Pediatric Hematology/Oncology* 21.3 (1999): 181-189.

7. Parham DM., *et al.* "Primary malignancies of bone and soft tissue in children and adolescents". *American Journal of Clinical Pathology* 115.1 (2001): S75-S96.

8. Park JR., *et al.* "COG high-risk neuroblastoma treatment update". *Journal of Clinical Oncology* 39.22 (2021): 2471-2482.

9. Matthay KK., *et al.* "Treatment of high-risk neuroblastoma with intensive therapy and 13-cis-retinoic acid". *The New England Journal of Medicine* 341.16 (1999): 1165-1173.

10. Yu AL., *et al.* "Anti-GD2 antibody with cytokines for neuroblastoma". *The New England Journal of Medicine* 363.14 (2010): 1324-1334.

11. Heczey A., *et al.* "CAR T cells for high-risk neuroblastoma: state of the art". *Frontiers in Immunology* 13 (2022): 876601.

12. Mosse YP., *et al.* "Targeting ALK-mutated neuroblastoma with lorlatinib". *Journal of Clinical Oncology* 37.15 (2019): 10009.