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SMALL ROUND CELL TUMORS PRESENTING AS ORBITAL PROPTOSIS IN CHILDREN WITH BONE MARROW INVOLVEMENT: A STUDY OF HAEMATO-MORPHOLOGICAL FEATURE.

Pathology

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ABSTRACT

Introduction: Childhood proptosis is an interesting clinical presentation of underlying hematological and non-hematological disorders. Malignant proptosis is most commonly caused by retinoblastoma, rhabdomyosarcoma, leukemia/lymphomas and other metastatic tumors such as neuroblastoma. Bone marrow examination is a commonly used diagnostic and staging modality in the evaluation of hematological and non-hematological disorders in pediatric population. Patients with proptosis present with subtle changes in hemogram which point towards metastatic or hematologic etiology and hence a detailed hematologic work-up is mandatory. **Aim/objective:** A descriptive cross-sectional study was conducted to study the clinical, hematological and pathological data of interesting pediatric malignancies presenting as orbital proptosis with or without bone marrow involvement at the time of diagnosis from July 2020 to June 2021. **Methods:** All cases of orbital proptosis presenting with cytopenias referred for bone marrow examination were included in the study. Primary diagnosis of was made on histopathology/fine needle aspiration cytology combined with clinico-radiological features. Bone marrow procedure was done from posterior superior iliac spine. The informed consents were taken from the patients in the vernacular language after explaining the procedures. All procedures performed in the current study were approved by Institutional ethical committee. Aspirate smears and biopsy sections were stained by May-Grunwald-Giemsa and Hematoxylin and eosin respectively as per standard protocols. Special stains Myeloperoxidase (MPO), Alcin blue, PAS (perioidic acid and Schiff) and reticulin were performed when required. Samples were also processed for molecular genetics studies in acute leukaemias. The descriptive analysis of the data was done, and the results were presented as mean, frequencies, and percentages.

Results: Of total 20 cases presenting as orbital-proptosis, only 11 cases showed bone marrow involvement as acute myeloid leukemia (45%) and as a metastatic site (55%). The most common cause of bilateral orbital proptosis was metastatic malignancies followed by acute myeloid leukaemias. Anaemia and thrombocytopenia were significantly ($p<0.05$) associated with marrow infiltration. **Conclusion:** The present analysis showed different types of pattern bone marrow infiltration had prognostic implications. Pancytopenias/bicytopeinias were most commonly seen in association with solid malignancies. Acute leukaemias presented with leukocytosis along with reduction in red cells and megakaryocytic lineages. Some cases primary diagnosis was initially made from bone marrow examination only. The present study highlights the significance of bone marrow examination in patients with proptosis wherein subtle changes in hemogram point toward metastatic or hematologic etiology.

KEYWORDS

Bone marrow, cytopenia, metastatic, leukaemias.

INTRODUCTION

Orbital lesions represent a varied group of lesions, including primary, secondary, and metastatic tumors [1, 2]. Proptosis is a common presenting symptom of orbital malignancies [1-4] The incidence of orbital malignancies in children and adolescents ranges from 8% to 18% of all orbital lesions [3-5]. The malignant round cell tumors (MRCTs) like rhabdomyosarcoma (RMS), retinoblastoma (RB) and primitive neuroectodermal tumour (PNET)/Ewing's sarcoma (EWS) account for majority of primary malignant tumors of orbit while acute myeloid leukemia (AML) is the commonest leukemia in both adults and children below 15 years presenting as metastatic malignancy in the orbit [6-8]. Bilateral proptosis is slightly more frequent in metastatic tumors than primary [9]. Bone marrow aspiration and biopsy (BMAB) gives a diagnosis for heterogeneous group of diseases involving hematopoietic cells and other diseases infiltrating the bone marrow [10]. Bone marrow examination is a commonly used diagnostic and initial staging modality in the certain pediatric tumors, such as neuroblastoma (NB), RMS, PNET/EWS [11]. Therefore, the present study was conducted to study hemato-morphological features of the cases presenting as orbital proptosis.

MATERIAL AND METHODS

A descriptive cross-sectional study was conducted to analyze clinico-hematological features of cases presenting as orbital proptosis from July 2020 to June 2021. Out of 250 cases during this period, only 20 cases presented with proptosis were studied. The study was undertaken after obtaining an Ethical Clearance from the Institutional Ethical Committee.

Inclusion Criteria:

Children upto18 years of age presenting with orbital proptosis and cytopenias referred for bone marrow examination were included in the study.

Exclusion Criteria:

The patients with bleeding disorders or who did not have orbital proptosis or who did not consent for the procedure were excluded from the study.

The informed consents were taken from the patients in the vernacular language after explaining the procedures. We studied detailed peripheral smear examination, bone marrow aspiration and biopsy findings along with clinical presentation of hematological and non-hematological tumors homing in and infiltrating the marrow. Primary diagnosis of malignant round cell tumors (MRCTs) was made on histopathology/fine needle aspiration cytology combined with clinico-radiological features. Bone marrow procedure was done from posterior superior iliac spine and bilateral trephine biopsies were performed. Subsequently, aspirate smears and biopsy sections were stained by May-Grunwald-Giemsa and Hematoxylin and eosin respectively as per standard protocols. Special stains Myeloperoxidase (MPO), Alcin blue, PAS (perioidic acid and Schiff) and reticulin were performed when required. Samples were also processed for molecular genetics studies in acute leukaemias. In all cases, routine morphological bone marrow details and counts, presence/absence of infiltration and its pattern were recorded. In addition peripheral blood counts, including, hemoglobin, total leukocyte count, platelet count and peripheral blood film morphology were also evaluated. Radiology was diagnostic in retinoblastoma and computed tomography scan (CT) of orbit showed intra-orbital mass with calcification and involvement of optic nerve along with cavernous sinus thrombosis. CT abdomen in neuroblastoma showed a large (8x5x3 cm) hemorrhagic necrotic mass in the right adrenal gland with central areas of calcification. In rhabdomyosarcoma, CT orbit showed retro-orbital enlarging hypodence mass with lytic lesion of orbital bones. The descriptive analysis of the data was done, and the results were presented as mean, frequencies, and percentages. The statistical analysis was performed using Microsoft excel 2010.

RESULTS

During the study period, 20 cases with isolated clinical presentation of orbital proptosis underwent bone marrow (BM) examination. Among non-hematological malignancies the maximum number of cases was of retinoblastoma (7), followed by RMS (3), NB (3) and EWS (2). Five cases had underlying acute myeloid leukaemia (AML) manifesting as proptosis. Of total 20, 11 cases showed BM pathology while in nine

cases BM was not involved. Patient's age ranged from 1-12 years with a mean age of 5.36 years. Of total 11 involved cases, six cases were ≤ 5 years of age and five cases were >5 years. The male to female ratio was 1.7:1. Bilateral proptosis was seen in seven cases (5 AML, 1 RMS, 1NB) and four cases had unilateral proptosis **(Table 1)**. Of total 15 cases of MRCTs, six cases (2 RMS, 2 NB, 1 EWS, 1 RB) showed marrow infiltration while nine (5RMSs, 3RBs, 1 EWS) did not show BM infiltration. In all cases of MRCTs the primary diagnosis was available either as histopathology and or as fine needle aspiration cytology of orbital mass. In one case, patient was diagnosed as MRCT on BM examination and then follow up was lost so final histopathological diagnosis could not be confirmed. Among hematological malignancies, five cases had underlying AML presenting as orbital propotosis without any appreciable hepato-splenomegaly or lymphadenopathy. The most common subtypes of AML were; AML-M2 (three cases), AML-M5 (one cases) and AML with t(8;21)(q22;q22).

Peripheral blood findings (Table 1):

Complete blood counts in involved cases showed that anemia was present in 81.8% cases, hemoglobin range = 67-125 g/L (median = 89 g/L); total leucocyte count was within the normal range in six cases (54.5%) and five cases had leuco-cytosis (45.5%), range = 6.1-45.3x10^9/L (median = 10.6x10^9/L); and platelet count below 150x10^9 /L (thrombocytopenia) was seen in 54.4% of cases, range = 30-455x10^9/L (median = 122x10^9/L). On evaluating overall cytopenias, bicytopenia was present in 45.5% cases and pancytopenia in none. Leuco-erythroblastic blood picture was present in seven cases (63.6%) (2MRCTs + 5AML). Immature circulating cells/myeloid blasts were present in all cases of AML. Average red cell indices were low in cases of MRCTs as compared to AML. In the uninvolved cases anemia was seen in three cases, leucopenia and thrombocytopenia in none.

Bone marrow findings (Table 1): In all cases, bilateral trephine biopsies and aspirate smears were examined. Both aspirate smears and trephine biopsy showed infiltration in all six cases of MRCTs. On aspirate as well as imprint smears, tumor cells were arranged in the form of small clusters and as singly scattered cells **(Figure 1 A, B, C, D, E, F)**. Rosette formation was seen in one case each of Ewing's sarcoma (EWS), neuroblastoma (NB), and retinoblastoma (RB). Trephine biopsy sections showed diffuse infiltration with near total replacement of marrow spaces in two cases, diffuse as well as interstitial pattern of infiltration in two cases and interstitial alone in two cases **(Figure 2 A, B, C, D, E, F)**. One case of RMS showed with extensive gelatinous marrow transformation highlighted by blue alciniphilic extracellular material with Alcin blue stain. In another case of EWS, PAS stain highlighted PAS-positive glycogen globules and trephine biopsy section showed extensive marrow fibrosis with osteomyelosclerosis along with diffuse infiltration (near-total replacement) and focal organoid pattern. Megakaryopoiesis was reduced in three cases of MRCTs and erythropoieisis was mildly megaloblastic in three cases. Cases of acute myeloid leukemia showed presence of ≥ 20% myeloid blasts in aspirate smears which were positive for myeloperoxidase stain **(Figure 3 A, B, C)**. Trephine biopsies sections in all cases of AML showed diffuse as well as interstitial excess of immature cells with marked reduction in erythoid and megakaryocytic series of cells **(Figure 3 D, E)**. Erythropoiesis was normoblastic in all cases of AML. Significant granulocytic and megakaryocytic dysplasia was noted in one case of AML with cytogenetic abnormaltiy t(8;21). Molecular genetics study was negative in all, except one case which was positive for t(8;21) on RT-PCR.

Follow Up And Treatment:

Of total five cases of AML, one patient with AML-t(8;21) refused treatment. Others were started on induction chemotherapy and received course 1 induction with cytarabine, daunorubicin and etoposide based on MRC AML XII protocol. AML-M5a did not achieve remission after 2 courses of induction and 1 course of high dose cytarabine consolidation with marrow showing 86% blasts. She is on palliative care. In one patient with AML-M2, course was complicated with Acinetobacter sepsis and she died around 2.5 weeks after first admission. One patient with AML-2 completed four courses of AML chemotherapy. Another patient with AML-M2 with VIIth nerve lower motor neuron palsy received 3 courses of AML chemotherapy and is due for course 4. Marrow post course 1 was in remission. He is doing well till now. Among MRCTs, two patients (one stage IV NB and other EWS) refused treatment. Another case of stage IV NB with supra renal mass with multiple bony metastasis and bone marrow involvement was started on treatment for high risk NB based on the SIOP protocol. Currently he is on differentiation therapy with 13 cis-retinoic acid and is doing well till date.

One patient with stage IVa retinoblastoma received neoadjuvant chemotherapy followed by enucleation. She is currently on local radiotherapy and planned for high dose chemotherapy with autologous stem cell rescue. Two patients with rhabdomyosarcoma died because of moribund status with extensive parameningeal involvement and neurological deterioration.

DISCUSSION

Bone marrow is one of the most common organs to be involved by tumors that metastasize via blood stream [6]. In children, MRCTs are a group of malignancies including neuroblastoma (NB), rhabdomyosarcoma (RMS), retinoblastoma (RB), Ewing's sarcoma (EWS) and acute lymphoblastic leukemia/lymphoma (ALL) that show a propensity to metastasize to bone marrow and account for the majority of marrow metastasis in children [6,7]. Bone marrow infiltration needs to be evaluated in all cases of MRCTs for clinical staging and risk assesment and if found to be involved, then categorised as high-risk group requiring a course of aggressive chemotherapy [12, 13].

In the present study we evaluated the hematological profile, bone marrow morphology and pattern of infiltration of hematological and non-hemtological malignancies presenting as orbital proptosis. Of total 11 cases, five cases had bone marrow as primary site of diagnosis and while in remainder six cases bone marrow was involved as the metastatic site. Both bone marrow aspirate smears and bilateral trephine biopsies were diagnostic in all cases (100%). Different types of pattern of infiltration were recorded on trephine biopsy sections and aspiration smears. In the present study rosettes were most commonly observed in cases of NB, RB and ES. In addition one case of RMS showed extensive gelatinous transformation of BM. One case of EWS showed grade 3 bone marrow fibrosis (3/3, EUMNENT) with extensive osteomyelosclerosis and near-total marrow replacement by tumor cells. The hematological abnormalities most suggestive of marrow infiltration were peripheral anemia (81.8%), thrombocytopenia (54.4%) and leukoerythroblastic picture (63.3%). Similar results have been observed by other studies [13-15].

Bone marrow metastasis in non-hematological solid tumors had been reported virtually in all types of malignancies both in Western and Indian literature [16-20]. According to a study, bone marrow involvement was highest in neuroblastoma (9/14), retinoblastoma (3/7), Ewing's sarcoma (14/47) and in rhabdomyosarcoma (5/20) [11]. Detection of metastatic tumor in the bone marrow is of great importance for the clinical staging, as it may influence the response to treatment and the overall survival. Bone marrow aspiration and bilateral trephine biopsies are relatively sensitive technique for detecting bone marrow infiltration by metastatic tumors [19]. Some studies showed that bone marrow aspiration smears were adequate in pediatric MRCTs [11]. The advantage of the trephine biopsy is that it preserves the histological architecture of the tumor cell [20-22]. The rosette formation and glandular structures can be frequently appreciated in the trephine biopsy section [23, 24]. In addition paraffin embedded sections can be utilized to do special stains and immunohistochemistry (IHC) for further typing. Certain tumor types which subtly infiltrate the bone marrow are difficult to detect on trephine biopsy section while the smear preparation helps in recognition of typical features of malignant cells. Therefore, the two procedures should be regarded as complimentary [23].

Bone marrow metastases by MRCT is not uncommonly encountered in pediatric patients and can present diagnostic difficulties especially in cases where, bone marrow disease is the sole primary manifestation, thus mimicking acute lymphoblastic leukemia. Cases of rhabdomyosarcoma mimicking acute leukemia have been described in the literature [20, 21]. We should therefore be vigilant while making a diagnosis of acute leukemia especially in those cases which on immunophenotyping show abnormal cells neither to be of B or T cell origin and do not show reactivity for myeloid antigens. In addition to considering the diagnosis of acute myeloid leukemias, possibility of metastatic tumors should always be kept in mind. A detailed work-up of such cases including detailed history and radiological findings, BMAB, extended panel of antibodies by IHC and relevant cytogenetic analysis should always be carried out to make a correct diagnosis [23].
EWS is the second most common bone tumor in children and

adolescents. Bone marrow involvement is a frequent event in metastatic EWS (52%) and is often multifocal and therefore requires extensive BM investigation [13, 22]. Metastatic disease is found in approximately 25% of patients at diagnosis [24].NB is overall the third most common solid malignancy of childhood (with median age of 17 months). Bone marrow infiltration needs to be evaluated in all cases of neuroblastoma for staging the disease [12, 23]. Retinoblastoma can also show BM infiltration and show various reactive BM changes including eosinophilia [13].

Myeloid sarcomas are rare extramedullary manifestations of AML, with an estimated incidence of 2.5-8% in AML. Orbital location is the most common [8, 24]. Myeloid sarcoma may be metachronous or synchronous to leukemia. In the case of orbital location, bilateral proptosis is slightly more frequent than unilateral proptosis. AML should be considered in the differential diagnosis of an orbital mass, even in the absence of typical leukaemic symptoms [24].

Imaging staging modalities techniques are usually ineffective and BMAB remain the procedures of choice to document BM involvement. Immunohistochemical studies as well as molecular techniques like polymerase chain reaction have enabled us to detect metastatic cells in the BM, even if they are in minute quantities [13, 24].

In our study bilateral proptosis was present in all cases of AML and one case each of RMS and NB. Thus, bilateral proptosis can serve as a reliable indicator to the probable diagnosis of a metastatic/ hematologic malignancy. Anemia and thrombocytopenia are the most common hematological abnormalities observed. Patients with proptosis present with subtle changes in haemogram which point towards metastatic or hematologic etiology and hence a detailed hematologic work-up is mandatory before imaging studies and invasive orbital biopsy embarked upon [24]. The demonstration of marrow involvement in early stage disease by application of newer technique is of interest. Immunohistochemistry, clonal growth, flow cytometry, fluorescent in situ hybridization & PCR techniques will indicate a greater frequency of tumor infiltration than has been evident from standard histological methods [23, 24].

CONCLUSION

The present analysis showed different types of pattern bone marrow infiltration had prognostic implications. Pancytopenias/bicytopeinias were most commonly seen in association with solid malignancies. Acute leukaemias presented with leukocytosis along with reduction in red cells and megakaryocytic lineages. Some cases primary diagnosis was initially made from bone marrow examination only. The present study highlights the significance of bone marrow examination in patients with proptosis wherein subtle changes in hemogram point toward metastatic or hematologic etiology.

Table 1: Clinico-haematological Characteristics Of The Patients (n=11)

Parameters	N=11
Age (years)	Range 1-12 (mean 5.36)
Orbital proptosis	Unilateral= 4MRCTs Bilateral= 7(5AML, 1RMS, 1NB)
Hepatoslenomegaly and lymphadenoapthy	Nil
Duration of symptoms	2 weeks-4 months
Radiology (Orbital CT scan)	Diagnostic in all cases of retinoblastoma
Haematological findings of the cases: Peripheral blood findings	
Hemoglobin (g/L)	Range 67-125 g/L (median = 89 g/L) Anemia in 9/11 cases (81.8%)
Total leukocyte count (x10^9/L)	Range 6.1-45.3X109/L (median = 10.6X109/L) Leucocytosis in 5/11 cases (45.5%)
Platelet count (x10^9/L)	Range = 30-455X109/L (median = 122X109/L) Thrombocytopenia in 6/11 cases (54.4%)
Leuko-erythroblastic blood picture	7/11 (63.3%)
Mean corpuscular volume (fl)	6 cases of MRCTs = mean 69.35; 5 cases of AML = mean 91.32
Bone marrow findings	
Cellularity	AML-Hypercellular; MRCTs-Normo-hypocellular
Erythropoiesis	AML-Normoblastic; MRCTs-Normo-megaloblastic
Megakarypoiesis	AML- Reduced; MRCTs-Adequate
Pattern of infiltration of MRCTs	AML-Diffuse sheets like; MRCTs-Variable pattern of infiltration
Follow up	

Abbreviations: MRCTs-malignant round cell tumors, AML-acute myeloid leukemia, RMS-rhabdomyosarcoma, NB-neuroblastoma, NA-not available.

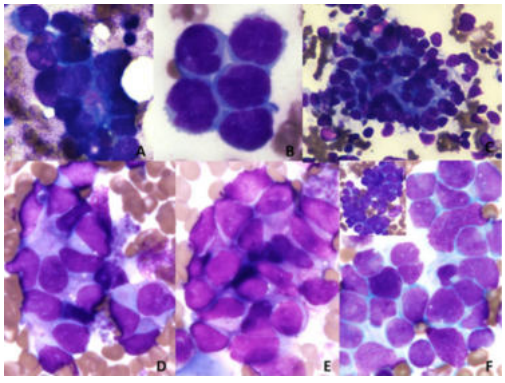

Figure 1 Photomicrographs (A & B) showing small clusters of tumor cells in Rhabdomyosarcoma exhibiting cleaved nuclear contours (Giemsa 200 and 400x) (C) Rossette formation in Ewing's Sarcoma (Giemsa 200) and (D & E) Neuroblastoma (Giemsa 400x) (F) Retinoblastoma: Small round blue cells exhibiting high N:C ratio (Giemsa 400x)

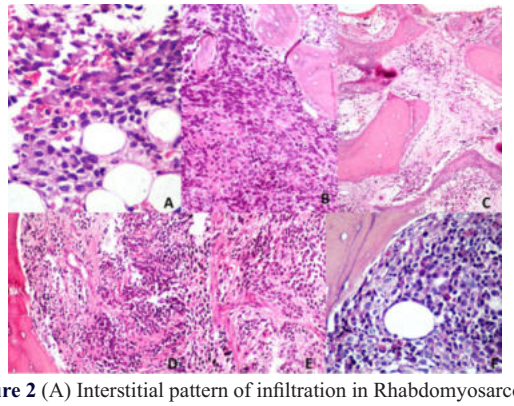

Figure 2 (A) Interstitial pattern of infiltration in Rhabdomyosarcoma (H&E, 200x) (B) Diffuse pattern in Retinoblastoma with rosette formation (H&E, 200x) (C) Areas of marrow fibrosis. (D & E) Diffuse infiltration by small round tumor cells in Neuroblastoma (F) Focal PAS positivity in Rhabdomyosarcoma (H&E, 400x) .

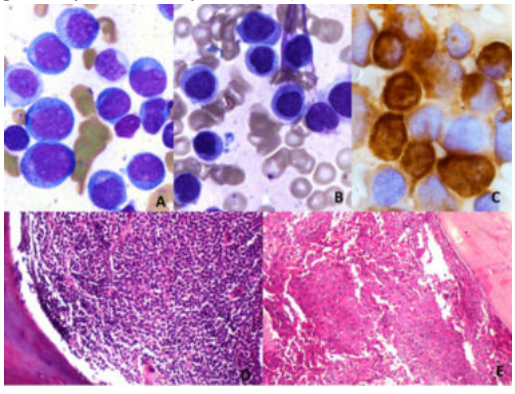

Figure 3 Microphotograph of bone marrow aspirate smears showing

(A) Myeloblasts with prominent nucleoli AML-M2 & (B) Cleaved irregular nuclear contours of blasts AML-5a (Giemsa, oil immersion) (C) MPO positivity in myeloblasts (D & E) Trephine biopsies showing diffuse infiltration by blasts AML-M2 and M5 (H &E, 400X).

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