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ORIGINAL ARTICLE

PROPTOSIS IN ACUTE MYELOID LEUKEMIA: AN UNDER RECOGNIZED PRESENTATION OF HEMATOLOGICAL MALIGNANCY

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ABSTRACT

OBJECTIVE: To determine the frequency of proptosis and associations of proptosis with demographic, clinical and hematological characteristics with acute myeloid leukemia (AML) in children.

METHODS: This descriptive study was conducted at Combined Military Hospital, Rawalpindi, Pakistan from January 2018 to July 2020. Patients of AML between 1-12 years of age who presented with and without orbital granulocytic sarcomas (OGS), selected by non-probability convenience sampling technique were evaluated for proptosis. Patients were classified into different subtypes of AML according to French-American-British (FAB) classification. Cytogenetic studies by karyotyping were done to identify different genetic abnormalities associated with AML. Kaplan- Meier survival analysis was used to analyze the overall survival of AML patients.

RESULTS: Out of 230 patients diagnosed with AML, 34 (14.78%) patients presented with proptosis. Mean age of presentation was 6.80±3.69 years, with male-female ratio of 2.1:1. Proptosis was unilateral in 19 (55%) and bilateral in 15 (45%) patients. Ten (29.40 %) patients presented primarily with proptosis while 24 (71%) patients presented with proptosis and systemic features of leukemia. Overall AML-M2 was found in 102 (44.3%) cases and other types were observed in 128 (55.6%) cases. Most common FAB AML subtype associated with proptosis was AML-M2 (n=26; 76%). Median duration of survival in AML patients with OGS was 867 days and as compared to 353 days in AML patients without OGS.

CONCLUSION: Proptosis is a frequent finding in children with AML. AML-M2 is associated with proptosis in children with AML. Survival in patients with OGS was better than patients without OGS.

KEY WORDS: Leukemia (MeSH); Myeloid (MeSH); Acute (MeSH); Orbital (MeSH); Systemic (MeSH); Survival (MeSH); Proptosis (Non-MeSH).

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INTRODUCTION

Leukemia is the most common hematological malignancy in children.[1] Among all pediatric leukemia patients, 18% present with acute myeloid leukemia (AML).[2] Fifty percent of all the pediatrics leukemia deaths have been attributed to AML with the survival rate of 64% in developed countries like United States.[3] Patients diagnosed with AML are extremely unfortunate as it not only exhausts the patient and their families physically and mentally but also have high financial implications. In the past AML was a difficult affliction to treat, but the treatment outcomes of pediatric AML have improved with advances in chemotherapy, hematopoietic stem cell transplantation and supportive care.[4]

AML usually presents with systemic manifestations like blood dyscrasias and fever, but it can rarely present with extramedullary granulocytic sarcoma also known as myeloid sarcoma (MS).[5] MS are soft tissue masses composed of tumor cells of myeloid origin and can occur in any part of the body like skin, soft tissue, kidneys, lymph nodes and subperiosteal regions of the bones including cranium, ribs, sternum, vertebrae, and orbits. One of the most common sites of MS is the orbit which is also known as orbital granulocytic sarcoma (OGS) and can presents clinically as unilateral or bilateral proptosis.[6] MS may either present as isolated phenomenon or may present concomitantly with systemic manifestation.[7] Patients with isolated MS present as diagnostic challenge in absence of systemic manifestation as it leads a physician to other more common diagnosis like lymphoma, rhabdomyosarcoma and neuroblastoma that can only be ruled out by tissue biopsy.[8] While isolated OGS with proptosis remains underappreciated presentation of AML and most of the data regarding it is based on western studies. The association of OGS presenting as proptosis with AML has very rarely been studied in our local population which needs to be investigated.

This study was conducted to find out the frequency and associations of proptosis with demographic, clinical and hematological characteristics in children with AML.

METHODS

This descriptive cross-sectional study was conducted in Pediatric Oncology department, Combined Military Hospital (CMH) Rawalpindi, Pakistan from January 2018 to July 2020 after approval from institutional review board and ethical committee. All the 230 AML patients admitted in Pediatric Oncology Ward CM) Rawalpindi were evaluated for proptosis on basis of history, examination, and investigations after informed consent from parents/ guardian. The diagnosis of AML was established by bone marrow biopsy and immunophenotyping by flowcytometry. The cases having no bone marrow

TABLE I: DEMOGRAPHIC AND CLINICOPATHOLOGICAL DATA OF PATIENTS WITH ORBITAL GRANULOCYTIC SARCOMA

Variable		With Proptosis Frequency (%)	Without Proptosis Frequency (%)	Total Frequency (%)	P Value
Age distribution	**< 5 years**	13 (38.20)	82 (41.8)	95 (41.3)	0.406
	5-9 years	11 (32.4)	76 (38.8)	87 (37.8)	
	> 9 years	10 (29.4)	38 (19.4)	28 (20.9)	
Gender distribution	**Males**	23 (67.60)	123 (62.8)	146 (63.5)	0.584
	Females	11 (32.40)	73 (37.2)	84 (36.5)	
WBC count (cells/mm^3)	**<50,000**	26 (76.5)	124 (63.3)	150 (65.2)	0.136
	≥50,000	8 (23.5)	72 (36.7)	80 (34.8)	
Types of AML (FAB classification)	**AML M2**	26 (76.5)	76 (38.8)	102 (44.3)	0.001*
	others	8 (23.5)	122 (62.24)	128 (55.6)	
Total		34 (100)	196 (100)	230 (100)	

involvement had incisional biopsy of ocular mass. All the AML patients, selected by non-Probability convenience sampling technique, both males and females, between 1-12 years who presented, were included in the study. Patients with Down syndrome, acute promyelocytic leukemia (APML) and secondary AML were excluded from the data analysis.

Data of all AML cases presenting with proptosis was collected for their demographic features (like age and sex), clinical presentation (including presenting symptoms and signs, isolated or concomitant presentation with systemic features and laterality) and hematological characteristics (like complete blood counts (CBC), subtype of myeloid leukemia according to FAB classification and cytogenetic abnormalities). Patients were classified into different subtypes of AML according to FAB classification. Cytogenetic studies by karyotyping were done to identify different genetic abnormalities associated with AML. All the data extracted from patient's history, examination and investigations was recorded on performa and was electronically formalized.

Data was analyzed using Statistical Package for Social Sciences version 23. Descriptive statistics were applied. Frequencies and percentages were used to analyze categorical variables and were compared using chi square test. Kaplan- Meier survival analysis was used to analyze the overall survival of AML patients who presented with proptosis and without proptosis.

RESULTS

Out of 230 patients diagnosed with AML, 34 (14.78%) patients presented with proptosis. Pertinent clinical and laboratory data of these 34 patients were reviewed. Out of the 34 patients, 10 (29.41%) patients presented primarily with proptosis while 24 (70.58%) patients presented with proptosis and systemic features of leukemia simultaneously. Out of the 10 patients who presented primarily with proptosis, 3 had no evidence of hematological involvement on peripheral blood film as well as on bone marrow biopsy. In these 3 patients' final diagnosis of AML was made on tissue biopsy and immunohistochemistry of the orbital mass. Proptosis was unilateral in 19 (55.88%) patients and bilateral in 15 (44.11%). Mean age of presentation was 6.80±3.69 years and median age was 7 years. While maximum number of patients presented in age group less than 5 year. Most common FAB AML subtype associated with proptosis was AML-M2 (n=26; 76%). A comparison of demographic and clinic-pathological variables is presented in Table I

Out of 230 patient, 217 patients (including 34 patients with proptosis and 183 patients without proptosis) had systemic manifestations. Fever, pallor, bruising and bleeding were common in all AML patients. In patients with proptosis, pallor was the most common finding which was observed in 23 (67.64%) patients followed by fever in 20 (58.82%) patients Fever, pallor and bruising was significantly more in patients without proptosis (Table II) .

CNS involvement was seen in 6 (17.64%) of patients as evidenced by presence of blast cells in cerebrospinal fluid analysis. Hyperleukocytosis was found in 26 (76.47%) patients with mean white blood cell count of 47.55±60.53 cells/mm^3.

Overall survival of the patients with proptosis was 50%. Median duration of survival in AML patients with OGS was 867 days as compared to 353 days in AML patients without OGS showing better survival associated with OGS using the Kaplan Meier survival analysis (Figure 1).

DISCUSSION

In this study it was found that proptosis has a significant association with AML as 14.78% of our patients were found to have it. Proptosis presented not only with systemic features but also as an isolated phenomenon and can precede the onset of systemic AML. Presence of OGS with AML was found to be a better prognostic sign as median duration of survival in patients with OGS was found to be 867 days as compared to the 353 days in patients without OGS.

GS is a known association of AML reported in 2.5-9.1% of patients in literature.[9] These are tumors of immature hematopoietic precursor cells of granulocytic series which are localized in extra medullary tissues. Histological identification and diagnosis of these tumors in children is difficult and can easily be misinterpreted as malignant lymphomas or other common poorly differentiated pediatrics tumors like neuroblastoma and rhabdomyosarcoma especially when they precede the development of systemic leukemia.[10]

GS can present at any age either before or after the development of systemic leukemia. A broad age range has been reported ranging from 1-60 years, but the median age of presentation as reported by other authors in pediatric population is 6 years and 8.8 years.[10,11] This is consistent with the findings

TABLE II: SYSTEMIC MANIFESTATION IN PATIENTS WITH AND WITHOUT PROPTOSIS (n=217)

Systematic Manifestation		Proptosis			P-Value
		Yes (%)	No (%)	Total (%)	
Fever	**Yes**	20 (58.8)	153 (83.6)	173 (79.7)	0.001*
	No	12 (41.2)	30 (16.4)	44 (20.3)	
Pallor	**Yes**	23 (67.6)	164 (89.6)	187 (86.2)	0.001*
	No	11 (32.4)	19 (10.4)	30 (13.8)	
Bruising	**Yes**	7 (20.6)	84(45.6)	91 (41.7)	0.007*
	No	27 (79.4)	99 (54.4)	126 (58.3)	
Bleeding	**Yes**	3 (8.8)	40 (21)	43 (19.1)	0.095
	No	31 (91.2)	143 (79)	174 (80.9)	
Lymphadenopathy	**Yes**	6 (17.6)	46 (24.7)	52 (23.6)	0.372
	No	28 (82.4)	137 (75.3)	165 (76.4)	
Bone Pains	**Yes**	5 (14.7)	29 (15.4)	34 (15.3)	0.92
	No	29 (85.3)	154 (84.6)	183 (84.7)	
Total		34 (100)	183 (100)	217 (100)	

observed in our study where median age of presentation is found to be 7 years.

Sex predominance has been described differently in different studies. In our study male predominance was observed (67.6%). Male predilection has been reported by Cavdar AO, et al.[12] But other studies have reported female preponderance.[9,10]

Orbits are the most favored site for extramedullary GS and proptosis/ exophthalmos is the most common clinical manifestation. OGS is reported in 9.3-36% of children with AML.[13] Our findings of 14.7% proptosis presentation in AML also fall in this range. It was present bilaterally in 45% of patients and unilateral manifestation was observed in 55% of patients. Murthy et al., reported unilateral presentation in 67% of patients and bilateral presentation in 33% of patients.[10] These findings are different from those observed in our study.

Although orbits are the most common site for GS in children. But other rare sites reported in literature are nasopharynx, middle ear, intestine, skin spine and central nervous system. One of our patients also had nasopharyngeal GS in addition to OGS and had dysphagia and breathing difficulty. Another patient had also middle ear GS and presented with facial nerve palsy and deafness. Previous studies have reported patients with Orbital and CNS GS has better prognosis as compared to non-orbital, non-CNS GS in pediatric population.[9,14]

Onset of OGS in relation to AML can be variable and its isolated manifestation may portend the development of underlying malignancy. Many such cases have been reported in past where isolated presentation of proptosis led to the diagnosis of AML.[8, 15] Bidar M, et al. reported in his study that 2 (7%) patients presented with proptosis prior to development of systemic disease and diagnosis of AML was established on incisional biopsy of orbital mass.[16] In our study isolated orbital presentation was observed in 10 (29%) patients who presented primarily with proptosis. Out of these, 3 patients had no evidence of systemic leukemia on clinical presentation as well as on investigations that is bone marrow biopsy didn't reveal any abnormality while other 7 patients presented primarily with proptosis without any clinical systemic features but further workup like CBC and BM biopsy showed evidence of AML. While 24 (71%) patients presented simultaneously with systemic leukemia. Concomitant presentation of proptosis with systemic manifestations was reported in 41.9% and isolated GS in 16% of patients by Aggarwal E, et al. He also reported that AML patients who presented with isolated OGS have better survival than those who presented simultaneously with systemic leukaemia.[9] Better survival in isolated proptosis has been linked to early recognition and diagnosis of disease resulting in early institution of treatment.

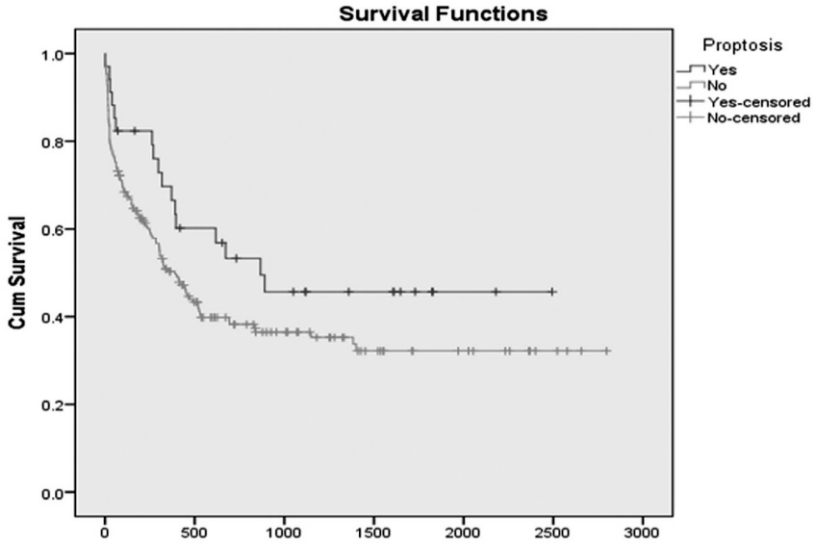

Figure 1: Kaplan Meier analysis curve

Mean duration of time to development of systemic leukemia has been reported differently in different studies. Cadaver reported 8 weeks and other series have reported it up to 1 year. Unusual delay in diagnosis of AML resulting in progression to systemic leukemia is associated with poor disease outcome and survival. So, a high index of suspicion is required by both the clinician and pathologist to make timely diagnosis.[10,12]

Variety of chromosomal aberrations have been identified in AML with extra medullary involvement, but the most common cytogenetics reported with OGS is t (8,21) in children. This translocation is associated with FAB M2 subtype. Previous studies have also reported the strong association of AML M2 and t (8,21) with orbital GS.[17] In our study the most common subtype of AML associated with proptosis was AML M2 and the most frequently

observed cytogenetic abnormality was t (8,21) translocation responsible for AML1 ETO fusion gene consistent with findings reported in literature. Presence of t (8,21) translocation in OGS is considered a good prognostic factor by many authors although some still believe that presence of this translocation and FAB M2 does not significantly alter the prognosis.[18,19] A recent study describes a 12p deletion in FAB M1 in OGS in adults. Other FAB subtypes previously reported to be associated with MS are M4, M5a and M5b.[9,20]

Prognostic value of presence of GS in AML is still controversial and there is limited data regarding the prognostic significance of GS. Although many studies have reported better prognosis in patients of AML with GS, and it is suggested that prognosis is even better when GS precedes the development of systemic leukemia (no bone marrow involvement). In such cases early diagnosis and initiation of treatment will improve the outcome of disease. Overall survival rate of AML patients with OGS in our study was 50% which was much lower than COG (children oncology group) report where OS was 92% in patients with OGS. [21] Mean duration of survival in Turkish study was reported to be 8.7 months in OGS patients and 28.6 months is non OGS patients which was in contrast to our findings.[17] Median duration of survival in AML patients with OGS was 28.5 months (867 days) while it was found to be 11.6 months (353) in patients of AML without OGS showing better survival associated with OGS in our study. Other studies have reported that extra medullary GS considered as a less favorable prognostic factor in AML and associated with poor disease outcome in terms of low remission rates, overall survival and increase chances of relapse.[22-25]

LIMITATIONS

Single center study and small sample size were the major limitation in this study. Secondly the better survival in patients with proptosis in our study, which contradicts the results of most of the other studies. Hence it requires multicenter studies, longer duration of follow up and larger sample size.

CONCLUSION

Proptosis is a frequent finding in children with AML. AML-M2 is associated with proptosis in children with AML. Survival in patients with OGS was better than patients without OGS.

RECOMMENDATIONS

Proptosis is an important sign of AML. Even in absence of systemic features patient should be promptly investigated for AML as proptosis can present as an isolated finding. This would require tissue biopsy and immunohistochemistry to prove or rule out AML.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

TF: Conception and study design, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical review, approval of the final version to be published

SK: Acquisition of data, drafting the manuscript, approval of the final version to be published.

TG: Study design, critical review, approval of the final version to be published.

MT: Conception and study design, acquisition of data, critical review, approval of the final version to be published

AA: Acquisition of data, critical revision, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST

Authors declared no conflict of interest

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DATA SHARING STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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