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Acute Promyelocyte Leukemia in A Child Presented With Proptosis: A Case Report And Literature Review

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Abstract: *Proptosis as a clinical manifestation of childhood acute promyelocytic leukemia is very rare. Only 15% of acute myeloid leukemia is seen in children and only 9.3%of it manifestated as orbital deposit causing proptosis in one or both eyes. We are here with reporting a case in a 8years girl who presented with fever and swelling of left eye in a case of acute promyelocytic leukemia. The purpose of reporting this case is to emphasize the need of examining the peripheral smear and bone marrow in children presenting as proptosis for early diagnosis of childhood AML. Here we have reviewed the last 40 years of Acute Promyelocytic Leukemia cases and articles regarding extramedullary involvement.*

Keyword: *Acute myeloid leukemia, acute promyelocytic leukemia, proptosis*

I. Introduction

Acute promyelocytic leukemia (APL) comprising 5-8% of all cases of Acute myelocytic leukemia (AML); is unique in its presentation in that it can cause coagulopathy and death if not readily diagnosed and treated. Morphologically it is classified as AML-M3 by French-American-British (FAB) classification. APL is typically characterized by neoplastic proliferation of Bone marrow with a pro-myelocyte phenotype along with balanced reciprocal translocation t(15,17)(q24.1;q21.2) which result in expression of promyelocytic leukemia(PML)-retinoic acid receptor α(RARA) fusion protein [1,3,5] . This fusion protein PML-RARA represses RARA and non-RARA target genes, resulting in uncontrolled proliferation and inhibition of cellular differentiation [4, 5]. Rarely the APL patients do not have an identifiable t (15, 17) by cytogenetic studies.1-2% of APL cases are due to rare variant translocations which typically involves RARA [1, 4, 6]. No APL variant with PML involvement alone has been identifiable to date. The variant translocations are ZBTB16/RARA, NUMA/RARA, STAT5B/RARA, PRKA1a/RARA, BCOR/RARA and FIP1L/RARA [7, 8].

As a special entity APL was first described in 1957 by a Swedish author, Hillestad [1] when he reported 3 patients characterized by very rapid fatal course with total WBC picture dominated by promyelocytes and severe bleeding tendency. He concluded that the disease seems to be the most malignant form of acute leukemia. More detailed features of APL were described by Bernard et al [2] in 1959. In 1973 Bernard et al [2] demonstrated that APL leukemic cells are sensitive to chemotherapy (Daunorubicin, Anthracyclin and Cytosine arabinoside) and the complete remission (CR) was 75-80% in newly diagnosed patients. In 1985, the introduction of ATRA (all Trans retinoic acid) came in the treatment of APL which raised the CR to 90-95% and 6 years Disease free survival (DFS) up to 86%.Basing on this APL is subdivided into 4 types- pre ATRA period (1957-85), introduction of ATRA (1985), use of ATO in APL (1990) and ATRA/ATO combination therapy. European APL group demonstrated in a randomized study that concurrent ATRA plus chemotherapy (DNR and Cytarabin) resulted in a lower relapse rate at 2 years(6%) when compaired with sequential ATRA followed by chemotherapy.[15,16,17,18,19]. Furthermore early addition of chemotherapy to ATRA decreases the incidence of retinoic acid syndrome [20].

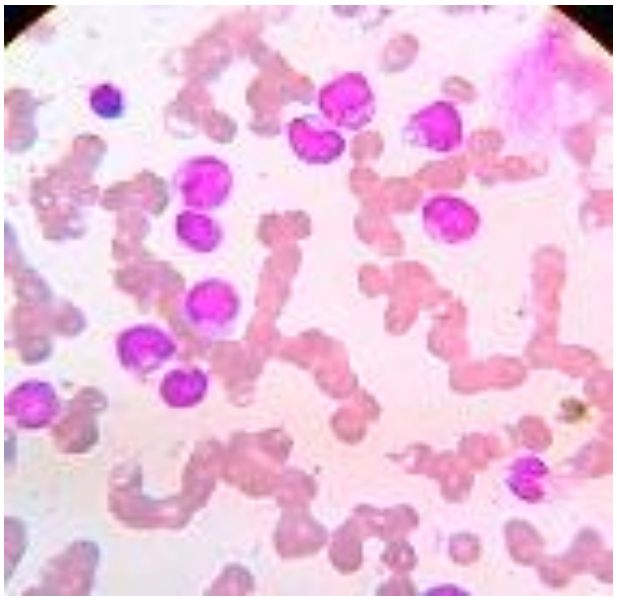
Clinically APL is more common in adult in their midlife and is very uncommon to diagnose APL before 10years of age. However a rare variant APL causes with t (5, 17) NPM/RARA have been diagnosed in pediatric patients [9]. The APL cases are generally present with leucopenia or pancytopenia, weakness and lethargy but extramedullary involvement like orbital proptosis is quite rare in APL. The early diagnosis of APL is imperative because it is associated with high risk of disseminated intravascular coagulation, a life threatening condition [11]. In our case we presented here a very unusual case of APL in a child with extramedullary orbital involvement.

CASE REPORT

[Fig1-proptosis of left eye]

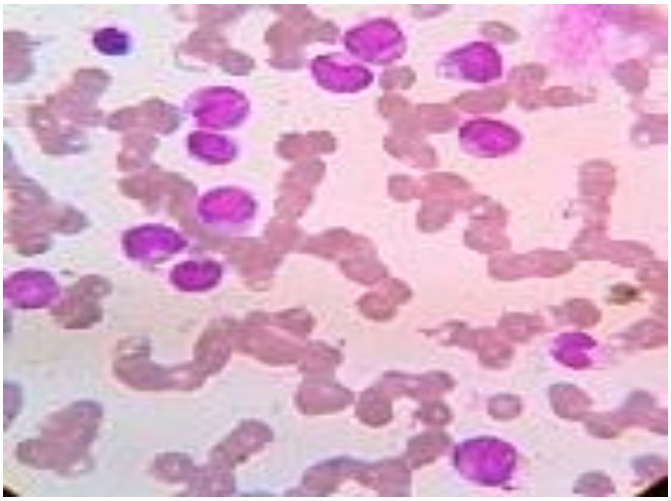
An 8year female child presented to ophthalmology OPD with history of fever and swelling of left eye for last 3months. On examination she was found to be anemic without having any petechial patches or any bleeding history. There was no organomegaly and no lymphadenopathy. Ophthalmologic examination revealed nonreducible axial proptosis of left eye without subconjunctival hemorrhage. There was no restriction of ocular movements in all directions [fig1].

On CBC, Hb=6.9gm%, TLC=11400/cmm, DC shows neutrophil=13%, lymphocytes=9%, eosinophil=2%, promyelocytes=64%, myeloblast=7% and myelo-metamelocyte=5%. Total platelet count was 50,000/cmm. In peripheral smear the promelocytes have folded or lobulated nucleus with cytoplasm containing numerous Auer rods and faggot cells.[fig2]



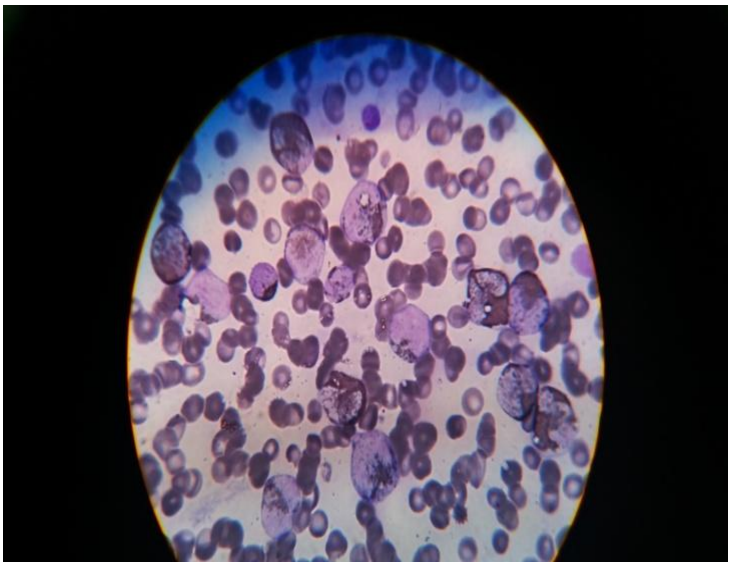
[Fig 2-P.S showing promyelocytes having Auer rods]

The Bone marrow aspiration shows hypercellular marrow with 13% blasts and 65%promyelocytes having bilobed nucleus and numerous Auer rods and foggots in their cytoplasm and cytoplasm containing coarse granules and M: E ratio is 10:1 confirming the diagnosis of acute promyelocytic leukemia, hyper granular variant in FAB-M3. [fig3]



[Fig 3-Promyelocytes showing Auer rods in BM]

The Sudan black-B staining was performed showing most of the blasts and promyelocutes being positive (about 80%). [fig4]



[Fig 4- Sudan black B positive cells]

The flow cytometry shows there was positivity of **CD45=99%, CD13=80%, CD33=88%, CD117=85%, CD34=83%,** with **CD56=88**% positive reflecting APL with bad prognostic sign.The cytogenetic study of this patient showed **t(15,17) translocation**,which confirmed the diagnosis of promyelocytic leukemia. Thus the patient was diagnosed as AML-M3 with extramedullary disease involving left orbit having bad prognostic index.

II. Discussion

AML with extramedullary involvement is otherwise known as granulocytic sarcoma .It is though very rare in occurrence but it may affect from infancy to old age. This tumor can present prior to or during the remission of systemic leukemia or it may present concomitantly [23][24].Among the extramedullary sites ,orbital proptosis is a common presenting feature[3].In our case ,the patient was noted to have orbital disease along with systemic leukemia. In cases where orbital involvement is initial presentation, the peripheral blood and bone marrow involvement usually occurs within a year of occurrence of orbital disease. Even though peripheral smear is quite suggestive of acute leukemia, but sometimes smear may not always be associated with precursor cells or blasts .Therefore bone marrow aspiration and biopsy should be advisable in all pediatric patients presented with orbital proptosis [24]. The promyelocytic leukemia morphologically classified as AML-M3 by FAB classification. This is characterized by proliferation of neoplastic cells of promyelocytic phenotypes in bone marrow along with balanced reciprocal translocation t (15, 17) which results in expression of PML-

RARA fusion protein [26, 23]. Usually APL is sensitive to ALL-TRANS-RETINOICACID (ATRA) and arsenic trioxide (ATO). 1-2% of APL cases are due to rare variant translocation which involves RARA but not PML. .So RARA (chomosome17) is constant translocation in all cases of APL.

Morphologically AML-M3 has 4 subtypes i.e.; hypergranular (classic M3), micro granular (M3V), promylocytic leukemia hyper basophilic and zinc finger/Retinoic Acid Receptor-α (M3r) [26] The classic hyper granular variety of APL, the bone marrow aspirate is hyper cellular and the abnormal promyelocytes constitute the predominant component. The cells are heavily granulated often obscuring the nucleus. Nucleus is bilobed and cytoplasm contains distinctive Auer rods and vacuoles. Sometimes flaming promyelocytes seen due to liberation of granules into surrounding matrix giving a reddish purple hue. The micro granular variant constitutes 20-30% of APL where the granules are less prominent and dispersed. In this case the peripheral total leukocyte count may be higher than the classic variant. The hyper basophilic variant is an uncommon form of APL where the cytoplasm is deeply basophilic and may have small blebs, buds or projections. Nucleus is lobulated and occupies most of the cell. The fourth variant is Zinc finger (PLZF)/RARA fusion product. These leukemic cells lack a folded or bilobed nucleus but have regular round or oval appearance. Auer rods are generally rare and cytoplasmic granularity is in intermediate between M3 and M2 of AML. [26] For diagnostic point of view though cytochemicals are not diagnostic of APL but they may help characterize them. The hyper granular variant stains intensely with SBB and MPO whereas the micro granular variety retains this staining pattern less intensely. The metachromatic staining with toludine blue has been reported in cases of APL with basophilic differentiation.

Immunophenotyping is also helpful in confirming the diagnosis of APL [26]. The cells express early myeloid marker CD33 but lack HLA-DR.CD34 is generally not expressed whereas CD13 is occasionally observed and possibly associated with development of retinoic acid syndrome(RAS).[26].CD56 ,the NK marker has been reported in true APL and associated with poor prognosis. Cytogenetically APL shows the balanced translocation between chromosome 15 and 17 in 95% cases which provides a definitive diagnosis of APL. This translocation results a fusion protein PML-RARA where PML has growth suppressor and proapoptotic activity and RARA functioning as transcription factor that mediates the effect of retinoic acid, which is necessary for normal myeloid maturation. So PML-RARA results in constitutive proliferation and inhibition of terminal differentiation [26]. Other variant translocations seen are PLZF-RARA t(11,17) where the blasts have more regular nucleus and coarse or fine or no granules in cytoplasm and they occasionally have condensed nuclear chromatin compared with classic APL. Another variant is t(5,17) is found to have predominant population of hypo granular promyelocytes where Auer rods are absent. Prognostically the t(11,17) has poor prognosis because this gene product is ineffective to retinoic acid and it shows poor response to ATRA whereas t(15,17) has better prognosis. Classical APL cases are treated with ATRA and ATO along with Anthracyclin which improves overall survival rate compared to chemotherapy with anthracyclin alone with up to 90% cure rates [5].

III. Conclusion

Acute promyelocytic leukemia is a unique and specific form of AML described as most malignant type and also on the other hand show excellent response to chemotherapy with combination of ATRA when diagnosed earlier and which is very uncommonly sometimes presented with extramedullary proliferation of neoplastic cells involving either one or both orbits .Simultaneous expression of proptosis with systemic acute promyelocytic leukemia in a child though very rare, still every child presented with proptosis should be thoroughly evaluated to rule out leukemia and to give early diagnosis and treatment to reduce the fatality.

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