Case Report

Pediatric Acute Promyelocytic Leukemia: A Rare Case Report

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Abstract

Acute Promyelocytic leukemia (APML) belongs to French American British (FAB) classification M3 subtype of acute myeloid leukemia & is characterized by t(15;17) and resultant PML-RARA fusion gene. APML accounts for 5-10 % in pediatric age group. Patients usually present with bleeding manifestations, weakness and increased propensity for disseminated intravascular coagulation. Extramedullary involvement is rare. It is a hematologic disease presenting as medical emergency and can be diagnosed with certainty by morphological examination of peripheral blood film & bone marrow aspirate to allow initiation of targeted therapy in order to reduce mortality. Patients with APML receive combination of all-trans retinoic acid (ATRA) & arsenic trioxide to induce terminal differentiation of blasts. We present a case of APML in a four years old child presented in the department of clinical hematology with pallor, lymphadenopathy and hepatosplenomegaly.

Keywords:

Disseminated intravascular coagulation, all-trans retinoic acid, hypergranular, microgranular, paediatric APML

Introduction

Acute Promyelocytic leukemia (APML) is the subtype of Acute Myeloid Leukemia (AML) in which percentage of blasts may be <20% but instead the bone marrow and peripheral blood smear demonstrate atypical promyelocytes.[1] APML is characterized by the balanced translocation t(15;17)(q24.1;q21.2) and the resultant PML-RARA fusion gene.[2]The presenting features of APML include profound coagulopathy & thrombocytopenia producing increased bleeding risk along with weakness & fatigue. There are two subtypes-(a) Hypergranular promyelocytic leukemia and (b) Microgranular variant form of promyelocytic leukemia. Majority of hypergranular subtype associated with leucopenia or normal white cell count with abnormal promyelocytes while total count is usually higher with many leukemic promyelocytes in peripheral blood smear in microgranular variant.[1] The diagnosis of APML is a medical emergency in order to minimize early death in these cases. APML is a rare entity in paediatric

age group which accounts for only 5-10% of paediatric AML & less than 2% of infants with AML.[3] Till date, no specific risk factors have been described in paediatric age group. Paediatric patients with APML have highest cure rates with an average overall survival near 95% and event-free survival of 90% due to combined use of all-trans retinoic acid and arsenic trioxide which causes terminal differentiation of blasts.[3]

Case Report

A four years old male child was presented in medicine OPD with complaints of fever and cough for 1 week. The fever was on-off, moderate in severity, not associated with chills & rigors and got relieved on medications. The cough was mild &non-productive. The child was vaccinated fully upto the age and had no known allergies. His family history was not significant. On physical examination pallor, lymphadenopathy & hepatosplenomegaly were present. Vital signs demonstrated BP 110/60 mm Hg, PR-106 bpm, temperature 38.0ºC and oxygen saturation 99% on room air. Blood tests including complete hemogram, blood urea & serum creatinine were performed. Blood urea & serum creatinine were within normal range (BU-19mg/dl &S.creat-1.0 mg/dl). The requisition for bone marrow aspirate (BMA) report and flowcytometry were received in the clinical hematology department. Peripheral blood film revealed hemoglobin (Hb)-6.5g/dl, total leukocyte count(TLC)- 57,000/cumm with 70% of blast cells, absolute platelet count(APC) -18,000/cumm and dimorphic blood picture.

Bone marrow aspiration smears were aparticulate and cellular revealing near total replacement of marrow with blast cells having high N:C ratio, fine nuclear chromatin, prominent nucleoli in some, nuclear indentation and scant to moderate amount of cytoplasm which was granular at places. Normal hemopoietic elements were markedly reduced. Few megakaryocytes were seen. On special stain, the blast cells were strongly positive for Sudan staining.

Flowcytometry was also performed revealing SSC/CD45 plot- 95% with blasts positive for CD117, CD64, cMPO and CD45(dim positive). Blasts are negative for CD19, CD34, CD10, CD7, sCD3, cCD79a, cCD3 and Tdt. Final diagnosis of Acute myeloid leukemia; Promyelocytic type was made.

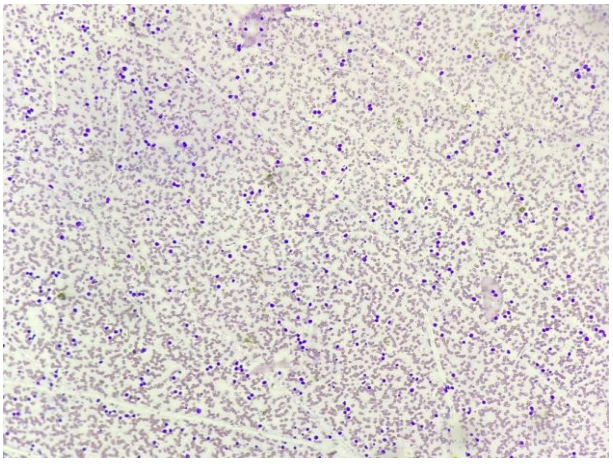

Figure 1 Peripheral Blood Smear showing increased total leucocyte count

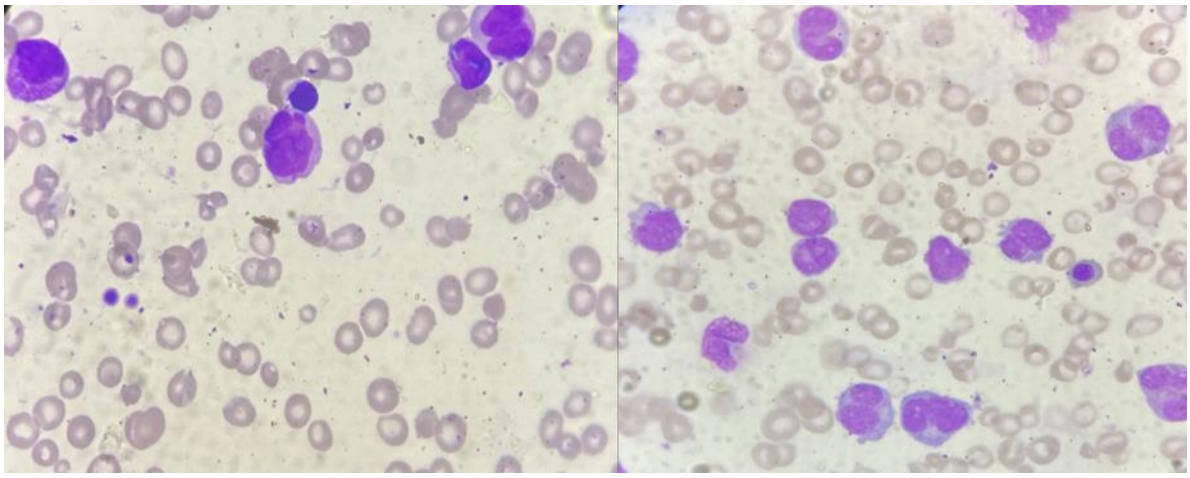

Figure 2 Peripheral Blood Smear shows atypical cells with bilobed nuclei (buttock-shaped), dimorphic cells & decreased platelet count

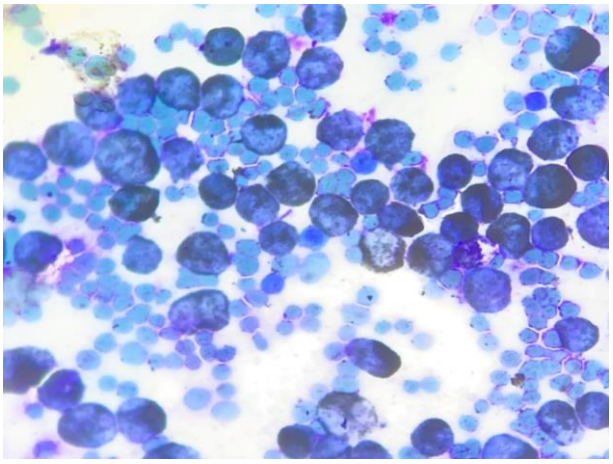

Figure 3 Sudan Staining shows strong granular positivity in the cytoplasm of these atypical cells

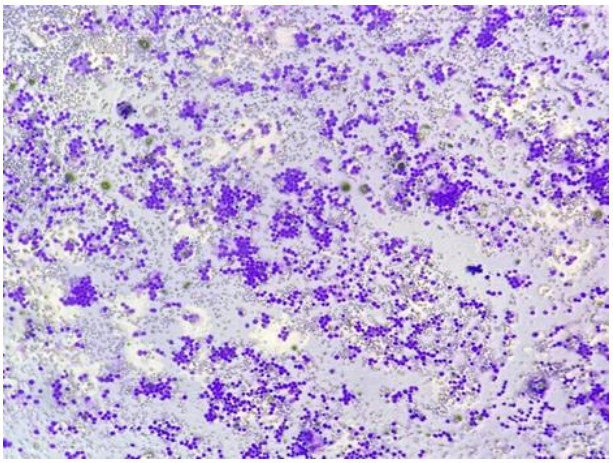

Figure 4 Bone Marrow Aspirate

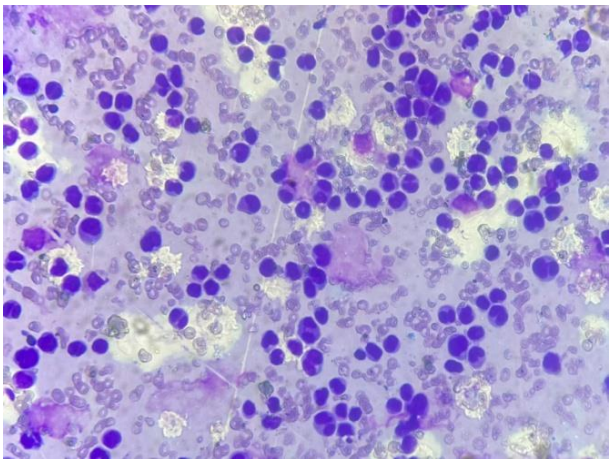

Figure 5 Bone Marrow Aspirate

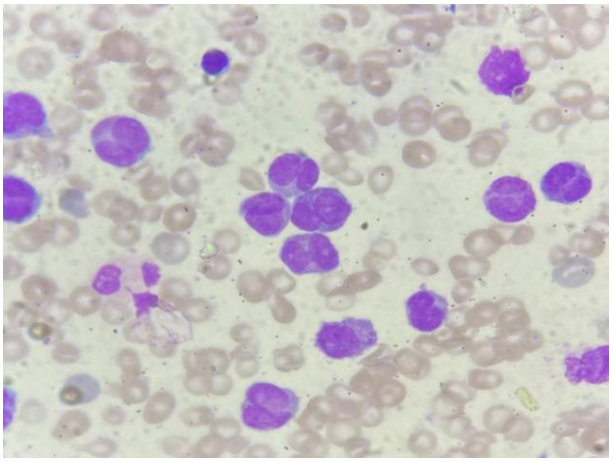

Figure 6 Bone Marrow Aspirate showing abundant atypical promyelocytes

Discussion

APML is a rare disease which comprises 10% of total cases of AML. In paediatric age group, the disease is rarer with 0.06 per 100,000.[4] The French American British M3 subtype of AML i.e.APML results from clonal proliferation of myeloid lineage cells that got arrested in promyelocyte stage. This maturation arrest results from a characteristic translocation between the PML gene on chromosome 15 & the RARA (Retinoic acid Receptor-alpha) gene on chromosome 17; t(15;17)(q22;q21.1). This translocation results in production of fusion protein PML-RARA which represses nuclear transcription, thus causing arrest at promyelocyte stage.[3]

There is a wide variation in the relative frequency of pediatric APML among worldwide population which attributes to the fact that environmental exposures and genetic susceptibility may influence breakage site involved in translocation. Further family history and exposure to various agents via occupation or other risk factors should be studied to explain the epidemiological variation.[5]

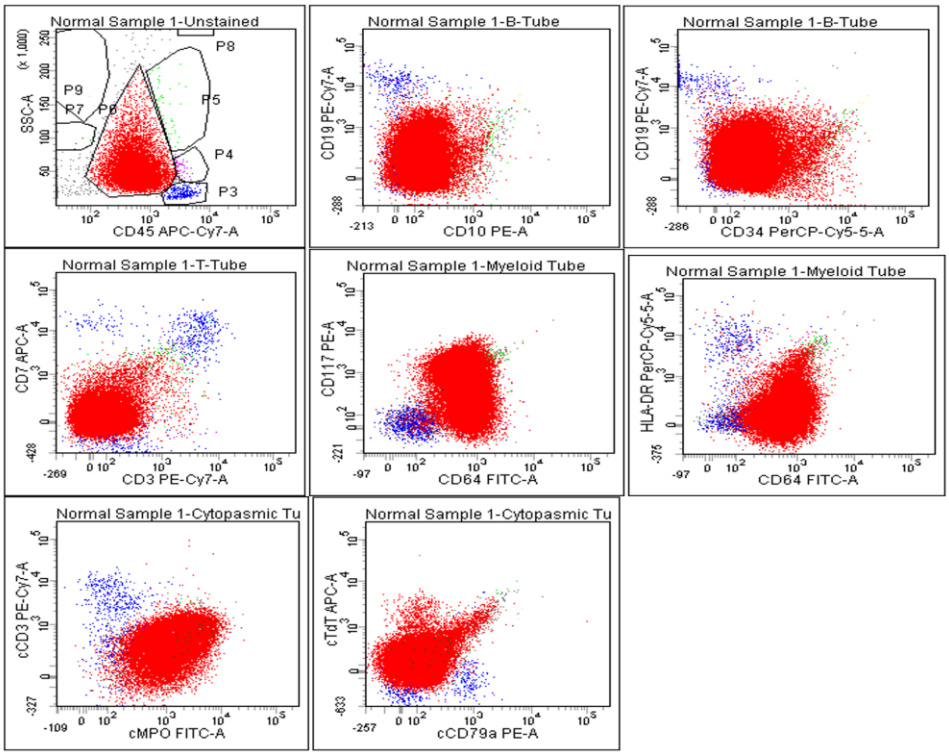

Figure 7 Acute Promyelocytic leukemia SSC/CD45 blasts positive for CD117, CD64, cMPO and CD 45 (dim to bright). Negative for CD19, CD34

On peripheral blood smear, the APML blast cells have a characteristic appearance with abundant cytoplasmic granules, bilobed/buttock shaped nuclei & prominent auer rods. The well-defined morphological features of blast cells along with immunophenotypic and molecular characterization have reliably allowed the identification of APML. Given the high mortality rate, treatment should be initiated as soon as APML is suspected based on clinical presentation and peripheral blood smear.[4]

Children with APML usually present with signs & symptoms of cytopenia like pallor, fatigue, bruising and fever. Extramedullary involvement such as hepatomegaly, splenomegaly and lymphadenopathy are less common in APML. The main distinguishing feature of APML is its propensity to cause disseminated intravascular coagulation (DIC). In 80-90% of APML cases, there is evidence of bleeding diathesis on initial presentation.[6]

ATRA therapy leads to improvement in coagulopathies in APML cases. The overall prognosis of APML is excellent with more than 90% patients achieving remission and 5 year overall survival rate in 80% patients.[7]

Conclusion

APML is a rare disease in pediatric age group. The characteristic presentation of typical leukemia accompanied with bleeding/DIC and the characteristic morphology on peripheral blood smear are important to recognize in order to initiate the targeted therapy and decrease the mortality from hemorrhagic complications.

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Competing Interests: None declared

Ethical justification: The study was conducted on samples received routinely in Department of Pathology, Pt. B.D.Sharma PGIMS, Rohtak. The study has not caused any harm to the patient. The confidentiality of the patient was maintained.

Informed consent: The study was conducted in the department of clinical hematology with informed consent.

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