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Acute Promyelocytic Leukemia in 9 Years Old Male Child-A Rare Case Report

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Abstract: Acute promyelocytic leukemia (APL) is rare in children. It is a subtype of leukaemia arising from a distinct reciprocal translocation involving chromosomes 15 and 17, which results in the *PML-RARA* fusion gene. ATRA (all-trans retinoic acid) /ATO (arsenic trioxide) is a drug of choice which induces complete remission in more than 93% patients of APML. For this early diagnosis and institution of therapy is important. Our patient 9 years male child presented clinically with ecchymosis and intermittently gum bleeding. From characteristic morphological findings in peripheral smear we reported the case as highly suspicious of APL-M3 and with the bone marrow and cytogenetic study the diagnosis was confirmed. Our patient then received treatment with ATRA/ATO. Following which there was clinical improvement and clearance of blasts and promyelocytes in follow up peripheral smears and bone marrow. It emphasizes the important role of hematology laboratory in the diagnosis and management of the disease.

Keywords: Acute promyelocytic leukemia (APML), acute leukemia, Hypergranular variant, ATRA/ASO.

INTRODUCTION

Acute promyelocytic leukemia (APL) is a rare form of acute myeloid leukemia (AML) comprising 5-8% of all cases of AML and 10% of de novo pediatric AML [1, 2].

Morphologically it is classified as AML-M3 by French-American-British (FAB) classification [3]. APL is characterized by neoplastic proliferation of cells in the bone marrow with a promyelocytic phenotype and the balanced reciprocal translocation t (15;17) (q24.1;q21.2), which results in the expression of the promyelocytic leukemia (PML)–retinoic acid receptor-a (RARA) fusion gene [4-7]. A number of variant translocations involving RARA gene have also been identified [4,6]. The disruption of the RARA gene results in maturation arrest of the myeloid progenitor at the promyelocytic stage and treatment with ATRA (all-trans retinoic acid) /ATO (arsenic trioxide) induction chemotherapy was able to induce differentiation and induce complete remission rates in more than 93% patients of APML. Thus there is dramatic improvement in clinical outcomes, transforming a previously deadly disease into highly curable one.

Clinically, patients frequently presents with weakness, fatigue, infection and bleeding due to leucopenia or pancytopenia.

We reported this case because occurrence of APML in the pediatric population is rare and it represents a true onco-hematological emergency. A prompt diagnosis of APL is vital as appropriate therapy must be started immediately to avoid the serious and potentially life-threatening complications associated with it. In this case it emphasizes the need of examining the peripheral blood smear and bone marrow in children presenting with gingival bleeding and ecchymois.

CASE REPORT

We report a case of an apparently healthy 9 year old male child who presented to the pediatric OPD with complains of chronic fatigue, ecchymotic patches on both the legs and intermittent gingival bleeding since 5 months. There was no history of fever, gross weight loss. On general examination, patient's vitals were stable, mild pallor and gross ecchymotic patches were noted over bilateral lower limbs. [figure1]. There was no significant finding on systemic examination. USG showed mild hepatosplenomegaly.

On complete blood examination, Hemoglobin was 7 gm%, TLC =11,600/mm^3, DLC= Neutophils-06%, Lymhocytes-16%, Eosinohils-02%, Myeloblasts-04%, Promyelocytes-68%, Myelocytes-02%, Metamyelocytes+Band forms- 02%
Platelet count = 30,000/mm^3
PT = 19.4, INR = 1.6

Peripheral blood smear showed many atypical promyelocytes having folded or lobulated nucleus with hypergranular cytoplasm and few with Auer rods and faggots [Figure2,3,4].

These findings were strongly suspicious of Hypergranular form of Acute Promyelocytic Leukemia. Thus, we advised bone marrow examination and cytogenetic study for its confirmation.

Patient was admitted and bone marrow was done. Bone marrow examination revealed hypercellular marrow with myeloid: erythroid ratio of 7:1 with myeloblasts -6%, and promyelocytes – 69%. Promyelocytes having bilobed nucleus, Auer rods and faggots with coarse eosinophilic granules in their cytoplasm confirming the diagnosis of Acute Promyelocytic leukemia, hypergranular variant, in FAB- AML- M_3.

Cytogenetic study confirmed t (15; 17) promyelocytic leukemia and PML: RARA gene translocation. The patient was then started on induction therapy with all-trans retinoic acid (ATRA).

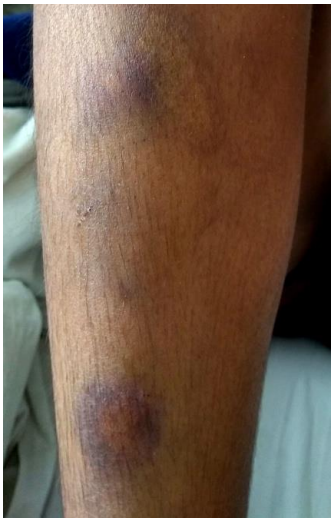

Fig-1: showing ecchymosis over lower limb

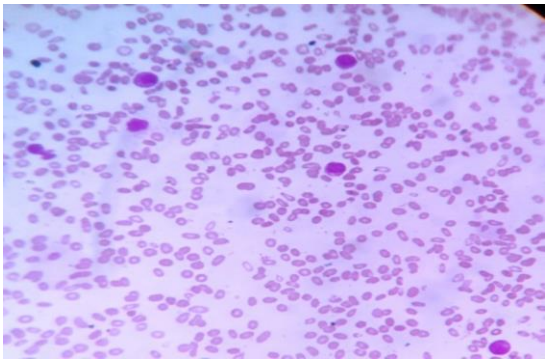

Fig-2: peripheral smear showing hypergranular atypical promyelocytes (Leishman stain;400X)

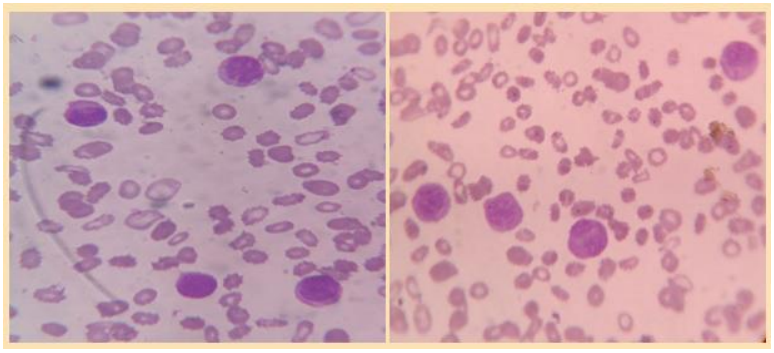

Fig-3&4: Peripheral smears showing atypical promyelocytes having folded or lobulated nucleus with hypergranular cytoplasm and few with Auer rods and faggots (Leishman stain; 1000X)

DISCUSSION

In children the APL is rare. APML results from clonal proliferation of myeloid lineage cells that are arrested at the promyelocyte stage. This maturational arrest results from a characteristic reciprocal translocation between the PML gene on chromosome 15 and the Retinoic Acid Receptor-alpha (RARA) gene on chromosome 17, t(15;17)(q22;q21.1). This translocation results in production of the fusion protein PML-RARA which represses nuclear gene transcription, arresting myeloid progenitors at the promyelocytic stage of maturation. However about 1% to 2% of APL cases are due to rare variant translocations, which typically involve RARA and RARA is assumed to have a key role in the pathogenesis of APL [4].

There are 2 morphologic variants of APL, hypergranular or ‘‘typical’’ APL and hypogranular or ‘‘microgranular’’ APL. Hypergranular APL comprises approximately 60% to 70% of cases of APL and presents with a low white blood cell count and abnormal promyelocytes with numerous red to purple cytoplasmic granules. Most cases have identifiable faggot cells with numerous Auer rods. While, hypogranular APL presents with leukocytosis, and numerous abnormal promyelocytes but the granulation is sparser and finer compared with the hypergranular variant. Faggot cells with multiple Auer rods are less commonly seen [3].

APML is strongly positive for Myeloperoxidase, Sudan black, PAS and Acid phosphatase is also strongly positive [7].

These cells frequently show immunopositivity for CD13 and CD33 antigens but do not express HLA-DR, CD34, and CD11b. In some studies the CD56 positivity at diagnosis is associated with poor outcome [5].

Children with APL usually present with the signs and symptoms of cytopenias common to other leukemias. Fatigue, pallor, bruising, and fevers are frequent complaints. 80-90% of patients with APML will have evidence of bleeding diathesis on initial presentation. Extramedullary diseases such as hepatomegaly, splenomegaly, and lymphadenopathy are seen less commonly in APL compared with other subtypes of AML, and CNS leukemia is rare [2].

Given the high upfront mortality rate, treatment should not be delayed pending molecular or immunophenotyping studies and should be initiated as soon as APL is suspected based on clinical presentation and/or the peripheral blood smear [2].

Our patient presented clinically with ecchymosis and intermittently gum bleeding as the signs of bleeding. From characteristic morphological findings in peripheral smear we reported the case as highly suspicious of APL-M3 and with the bone marrow and cytogenetic study the diagnosis was confirmed. Our patient then received treatment with ATRA/ATO. Following which there was clinical improvement and clearance of blasts and promyelocytes in follow up peripheral smears and bone marrow.

All-trans retinoic acid (ATRA), a vitamin A derivative, binds to the RARA site of the PML-RARA fusion protein in APL cells and allows the leukemic promyelocytes to differentiate into mature granulocytes[2,4].

The overall prognosis of APL is excellent and despite the fact that APL has a high risk of coagulopathy and hemorrhagic complications, the prognosis for treated patients able to achieve complete remission is better than that for any other category of AML, with more than 90% of patients achieving complete remission and 5- year overall survival rates in excess of 80%. On average, coagulopathy in APL corrects within a median time of 4 days after the initiation of ATRA [2].

CONCLUSION

Over the past three decades, APML has been transformed from a highly fatal disease to a highly curable one. This drastic improvement is because of the introduction of a new treatment strategy with all-trans retinoic acid and, more recently, arsenic trioxide. However to achieve this, early diagnosis is essential which will lead to initiation of disease-targeted therapy immediately.

Because of its characteristic morphology on peripheral blood smear, it is possible to recognize it in short time. This case report emphasizes importance of high index of suspicion of APML on peripheral blood smear examination by pathologist in timely diagnosis, its management and outcome

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