

## CASE REPORT

# Acute Promyelocytic Leukemia (APML) in A Four Year Old Child: A Case Report

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### Introduction

Leukemia is the most common malignancy of childhood representing about 30 % of oncohematological diseases diagnosed in children less than 15 years of age. Acute myeloid leukemia (AML) in paediatric field represents the 15-20% of oncohematological disease and the related mortality is approximately 30%. Among paediatric AML the incidence of acute promyelocytic leukemia (APML) is <10%.<sup>1</sup>

The genetic hallmark of APML is the balanced reciprocal translocation of (15:17) (q24;q21), leading to the fusion of promyelocyte (PML) gene with the retinoic acid receptor alpha (RARA) gene. The resulting PML-RARA hybrid oncoprotein is responsible for the block of differentiation of leukaemic promyelocytes and is able to induce leukaemia.<sup>2,3</sup>

The disease is frequently accompanied by a consumptive coagulopathy with life threatening haemorrhages (most severe one occurring in brain and lungs) and more rarely thrombosis. A rapid diagnosis of APML and the initiation of adequate anti leukaemic and supportive therapy are of paramount importance to prevent early death, which is currently considered the most important obstacle to the final cure of this disease. With the introduction of differentiation therapy with ATRA combined with conventional chemotherapy and the subsequent advent of ATO, APML has been transformed from the most rapidly fatal to the most frequently curable form of acute leukemia with long time survival rates up to 90%.<sup>4</sup>

### Case Report

A four-year old girl presented at Dr. MR Khan Shishu Hospital and Institute of Child Health with history of gradual pallor and high grade continued fever for

two weeks. On examination she was anaemic, febrile and her O<sub>2</sub> saturation was 98%. She had bony tenderness, bilateral cervical lymphadenopathy, hepatomegaly and gum hypertrophy (Fig 1) with significant bleeding gums with extensive bruising and petechiae located in the lower limbs.



**Fig 1** Gum hypertrophy of the child

The complete blood count (CBC) showed severe normocytic normochromic anemia (Hb - 4.9 g/dl), severe thrombocytopenia (PLT -  $15 \times 10^3$  / $\mu$ l) and leukocytosis (WBC -  $37 \times 10^3$  / $\mu$ l) with neutropenia (Neutrophils -  $0.41 \times 10^3$  / $\mu$ l). The peripheral blood film (PBF) showed several blasts (43%) with small and stubby cytoplasmatic auer rods, bilobbed nucleus with atypical appearance of internuclear bridge (Fig 2). Prothrombin time was 15 s (control 14 s), activated partial thromboplastin time (APTT) was 38 s (control 34 s) and fibrinogen was 1.5 g/L (2-4 g/L).

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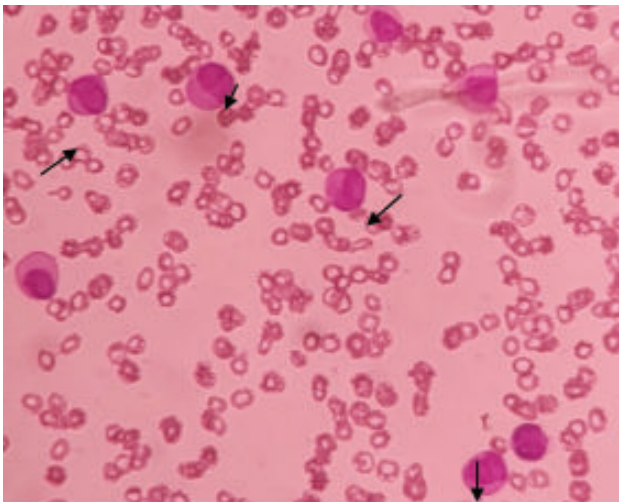
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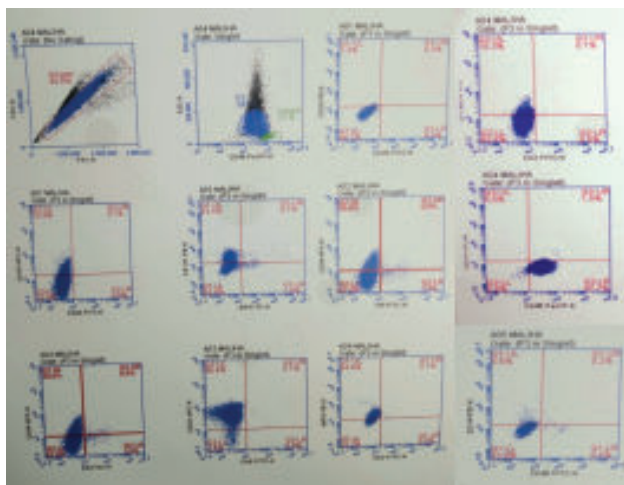
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Bone marrow was hypercellular with >90% atypical cell. The blasts have enough cytoplasm with granules and occasional faggots, loose chromatin with 1-3 nucleoli resembling atypical promyelocytes which give evidence for APML-M3. Flowcytometry (Fig 3) revealed a predominant CD 45 (98.7%) population which are positive for myeloid cell markers CD 13 (76.7%), CD 33 (96.5%), CD 117 (44.2%), MPO (64.7%) and precursor marker Cd 34. PML-RARá was detected in the bone marrow aspirate by RT-PCR.

So the child was diagnosed as a case of APML (PML-RARA positive). Treatment was started immediately with conventional ATRA and ATO protocol and prophylaxis with dexamethasone for differentiation syndrome. Supportive management including blood transfusion was given accordingly.



**Fig 2** PBF of the child with APML showing blast with bilobed nucleoli



**Fig 3** Flowcytometry of the child with APML

## Discussion

APML was first described in late 1950s in Norway and France as a hyperacute fatal illness associated with hemorrhagic syndrome.<sup>5</sup> Over the last few decades, APML has been transformed from a highly fatal disease to a highly curable one.<sup>6</sup> APML, the French-American-British (FAB) M3 subtype of AML, results from clonal proliferation of myeloid lineage cells that are arrested at the promyelocyte stage. So the defect is in normal granulocyte cell maturation and apoptosis. A gene translocation occurs in an abnormal cell between chromosome 15 and 17 in between the retinoic acid receptor, or RARA (RARá) and the promyelocytic gene, or PML gene, which is active in cell death and tumor suppression.<sup>7</sup> This unique break point allows for three isoforms of the gene, the most typical of which is t(15;17) (q22; q21).<sup>8,9</sup>

Children with APML usually present with the signs and symptoms of cytopenias common to other leukemias. Fatigue, pallor, shortness of breath, fever and bleeding manifestation like bruising, and petechiae of the mouth and other parts of the body are frequent presentation.<sup>10</sup> Our patient presented with the fever, pallor and bleeding manifestations. Extramedullary diseases such as hepatomegaly, splenomegaly, and lymphadenopathy are seen less commonly in APML compared with other subtypes of AML, and CNS leukemia is rare.<sup>11</sup> Gum hypertrophy is a common finding.<sup>12</sup> Our patient also presented with gum hypertrophy.

The central distinguishing feature of APML, as compared to other forms of leukemia, is its propensity to cause disseminated intravascular coagulopathy (DIC). 80-90% of patients with APML will have evidence of bleeding diathesis as well as intracranial haemorrhage on initial presentation.<sup>13,14</sup> Secondary infections like *Candida albicans* in the oropharyngeal area and Varicella zoster virus can appear in pediatric APML patients as well as localized soft tissue infections of herpes simplex virus can also occur.<sup>12,15</sup>

CBC typically reveals a lowered hemoglobin, hematocrit and leukocytosis or pancytopenia. PBF indicates a significant population (at least 20%) of large promyelocytes of hypergranular or microgranular bilobed form.<sup>16,17</sup> Our patient had leukocytosis with thrombocytopenia and also bilobed form of blast in blood film. The presence of Auer rods is also a significant clue. Severe coagulopathy and DIC are evidenced by lowered fibrinogen, overproduction of plasmin, elevated FDP and Ddimer

and increased prothrombin or thromboplastin times.<sup>18</sup> Bacterial and fungal cultures may be necessary to identify infections. CSF studies may also be recommended for high white blood cell counts to evaluate cellular movement in the body.<sup>18</sup>

In suspected APLM with t(15;17), a bone marrow biopsy and aspirate should be quickly obtained for cellular differentials, histology studies, myeloperoxidase activity, and cell antigen marker testing.<sup>19</sup> Morphologically over 25 % of paediatric APLM appear as microgranular variant.<sup>19</sup> In flow cytometry studies, a single major cluster population with a wide range of side scatter on a scatter dot plot suggests an APLM profile.<sup>20</sup> Cellular antigen CD33, co-expression of CD13, lack of or weak HLA-DR, and CD34 are also further evidence of the atypical population.<sup>20</sup> For molecular confirmation, samples should be sent for investigation with FISH probing to search for the typical translocation and also for cytogenetic studies to look for an abnormal chromosomal karyotype.<sup>16</sup> Quantitative PCR results of the gene transcript ratio also serves as a positive confirmatory procedure. Because the classic t(15;17) translocation creates two fusion genes from one splice, 70% of cases with translocation, harbor a RARA/PML gene, and 100% show the reciprocal PML/RARA gene.<sup>20</sup> This makes qPCR a useful assay for disease screening.

Treatment of APLM with t(15;17) is different from other variations of AML in that it is the only one with a target specific therapy.<sup>16</sup> The use of all-trans retinoic acid (ATRA) initiates differentiation of the immature myeloid cells and helps manage coagulopathy.<sup>7</sup> This vitamin A derivative releases repressor complexes from the RARA receptor fusion gene, thus help to get rid the blood of promyelocytes and their destructive granular material which contributes to DIC.<sup>16</sup> Patients undergoing ATRA treatment are at risk for differentiation/retinoic acid syndrome.<sup>12,15</sup> This syndrome is thought to arise from inflammatory cytokines released from inducing maturation of promyelocytes with ATRA from treated cells.<sup>21</sup> Symptoms are fever, respiratory distress, weight gain, pleural and pericardial effusions, hypotension, and/or renal failure.<sup>15,21</sup> Pediatric patients are particularly at risk for pulmonary edema.<sup>15</sup> Treatment of this entity consists of discontinuation of ATRA, administering dexamethasone and providing cardiorespiratory support.<sup>22</sup> In our patient we started Dexamethasone for prophylaxis of differentiation syndrome.

In addition to ATRA, use of arsenic trioxide (ATO) has also shown effectiveness in improving prognosis. It has become an additional standard of care since 2000, especially in patients with ATRA resistance and relapsing cases.<sup>23</sup> Arsenic trioxide is a destructive therapy for the abnormal fusion protein, and aids in marking the oncoprotein for degradation.<sup>7</sup> It functions similarly in advocating cell differentiation and apoptosis. APLM with high risk patient should be treated with additional chemotherapy because cell differentiation and remission is not long-lasting.<sup>16,20</sup> Possible chemotherapeutic drugs to support ATRA and ATO therapy include anthracycline and cytarabine.<sup>20, 24</sup> In conjunction with chemotherapy, aggressive therapy of DIC should be undertaken. Fresh frozen plasma and/or cryoprecipitate should be transfused to maintain fibrinogen levels over 150 g/dL and platelets should be transfused to maintain platelet counts over 50 x10<sup>9</sup> /liter. Heparin has not been demonstrated to have a clear benefit and is not recommended for DIC related to APLM.<sup>25</sup>

The overall prognosis of APLM is excellent, with more than 90% of patients achieving complete remission and 5-year overall survival rates in excess of 80%.<sup>26</sup>

### Conclusion

Acute promyelocytic leukemia (APML) is one of the few hematologic diseases that can be diagnosed with certainty by morphological examination of blood film and bone marrow aspirate by the practicing hematologist. However, whenever APLM is suspected based on clinical presentation and/or peripheral blood smear, disease-targeted therapy should be initiated as soon as possible to reduce the mortality from APLM.

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