# A Curious Case of Atypical Acute Promyelocytic Leukaemia in a 4-Year Boy

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## ABSTRACT

A 4-year boy presented with a history of fever, bruises, frequent transfusions, and left eye proptosis for 1 month. His baseline bone marrow biopsy and immunophenotyping by flow cytometry were consistent with acute promyelocytic leukaemia (APL), but bone marrow cytogenetics were consistent with variant translocation, a non-classical translocation involving chromosome 15 but with different fusion partners than t(15; 17). He initially did not respond to the high-risk APL induction protocol. Later, he was given a high-risk AML induction protocol, to which he responded, but due to financial constraints, the family could not opt for a curative haplo-identical bone marrow transplant, and eventually, the child died. This is the first case of APL with such a variant translocation documented in Pakistan. It is important to document such cases to gather their data, discuss the effectiveness of attempted treatments, and analyse subsequent responses.

**Key Words:** *Acute promyelocytic leukaemia M3, Promyelocytic leukaemia; retinoic acid receptor alpha, t(15; 17), Myeloid leukaemia, All-trans retinoic acid, Auer rods*.

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## INTRODUCTION

Acute promyelocytic leukaemia (APL) with promyelocytic leukaemia; retinoic acid receptor alpha (*PML; RARA*) fusion is categorised under acute myeloid leukaemia (AML), with defining genetic abnormalities according to the revised 5th edition of the World Health Organization Classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms.[1] The most frequent (>95%) rearrangement is between *PML* (part of chromosome 15) and *RARA* (part of chromosome 17), leading to *PML: RARA* fusion gene, *i.e.*, t(15; 17), and hence this remains the basic WHO criteria for its classification.[2] The identification of the *PML: RARA* chimeric gene is important, as this gene is sensitive to chemotherapeutic agents, all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), and has a high cure rate (*i.e.*, around 80%).[3]

Many cases lacking this classic translocation of *PML: RARA* have been identified as having classical morphology of APL, *i.e.*, abnormal promyelocytes/blasts with multiple Auer rods as shown in Table I.[4] The identification of these molecular variants of APL is important, as they have a variable sensitivity to the standard treatment of APL, *i.e.*, with ATRA and ATO.[5]

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The authors report a case of a 4-year boy, who presented as APL morphologically but with a complex karyotype and a non-classical translocation of chromosome 17, he did not respond to the standard treatment, *i.e.*, ATRA/ATO.

**Table I: Non-classic *PML RARA* translocation types.**

| **APL translocation types {other than classic *PML RARA* t(15; 17)}** |
|---|
| t(11; 17) (q23; q21) |
| t(5; 17) (q35; q21) |
| t(11; 17) (q13; q21) |
| der(17) |
| t(17; 17) (q21; q24) ordel(17) (q21; q24) |
| t(4; 17) (q12; q21) |
| t(X; 17) (p11; q21) |
| t(2; 17) (q32; q21) |
| t(3; 17) (q26; q21) |
| t(7; 17) (q11; q21) |
| t(1; 17) (q42; q21) |
| t(1; 17) (q42; q21) |
| **AML resembling APL with no *RARA* gene implication** |
| *NUP98-RARG*transcript |
| *PML-RARG* |

*APL, Acute promyelocytic leukaemia; PML; RARA, Promyelocytic leukaemia; retinoic acid receptor alpha; Der, Derivative; NUP, Nucleoporin; RARG, Retinoic acid receptor γ.*

## CASE REPORT

A 4-year boy presented with a history of fever, frequent transfusions, and left eye proptosis for 1 month. His complete blood count showed haemoglobin of 8.2 g/dL, white blood cells of 42 × $10^9$/L, and platelets of 12 × $10^9$/L. His peripheral blood smear and bone marrow revealed diffused infiltration with around 70% abnormal promyelocytes/blast cells; few of them exhibited multiple Auer rods (Figure 1). Immunophenotyping by flow cytometry on bone marrow aspirate comprised of 72% abnormal population expressing CD45 with high side scatter,

CD13+, CD33++, CD38+, MPO+, CD117– to +, and CD34 dim + with negative HLA-DR. His bone marrow cytogenetics showed 44, XY, t(1; 17) (p36.1; q21), add (4) (q12), -5, del (6) (q13; q23), der (7) ,t(4; 7) (q25; q32), -9, add (9) (p24), add (21) (q22),~15d-m;~28dm; abnormal male karyotype (Figure 2). *PML: RARA* translocation t(15; 17) was not detected on FISH. Based on morphology, flowcytometry, and complex karyotype with non-classical chromosomal 17 translocations, the case was diagnosed as atypical APL.

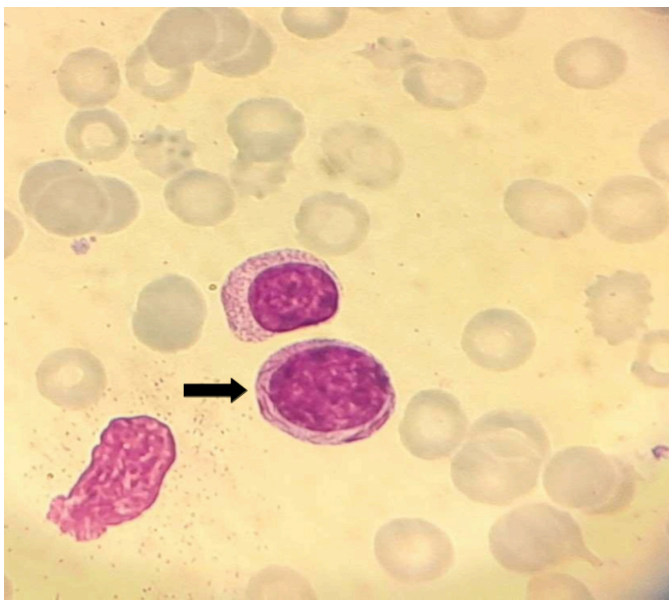

**Figure 1: Abnormal promyelocytes showing multiple Auer rods (arrow).**

Based on the discussion in the multidisciplinary team (MDT) meeting, he was started on high-risk induction chemotherapy for APL with ATRA, ATO, idarubicin hydrochloride, and prednisolone. Cerebrospinal fluid (CSF) cytology was not performed before initiating the treatment. The patient's post-induction day-60 bone marrow was consistent with the persistence of residual disease, and bone marrow cytogenetics remained unchanged. He had now developed bilateral scrotal swelling, which on ultrasound revealed enlarged testes with multiple ill-defined lesions suggestive of leukaemic infiltration. Post-induction, CSF cytology was performed, and it showed involvement with underlying malignant disease. The consolidation chemo-therapy was held, and re-induction chemotherapy as per the high-risk AML protocol was started.

After re-induction treatment according to the high-risk AML protocol, the patient's bone marrow and CSF showed morphological and molecular remission with resolution of the testicular swelling. Later, he was given two cycles of fludarabine-idarubicin (FLA-Ida). Meanwhile, his siblings' HLA typing for bone marrow transplant was sent. Unfortunately, none of his siblings had a full HLA match with him. The family was counselled and was given an option of referral to another specialised hospital in the country for haplo-identical bone marrow transplant, which was refused by the family due to financial constraints. Unfortunately, after the 2nd cycle of FLA-Ida, the patient relapsed with circulating blasts in the peripheral blood and CSF, and he eventually expired.

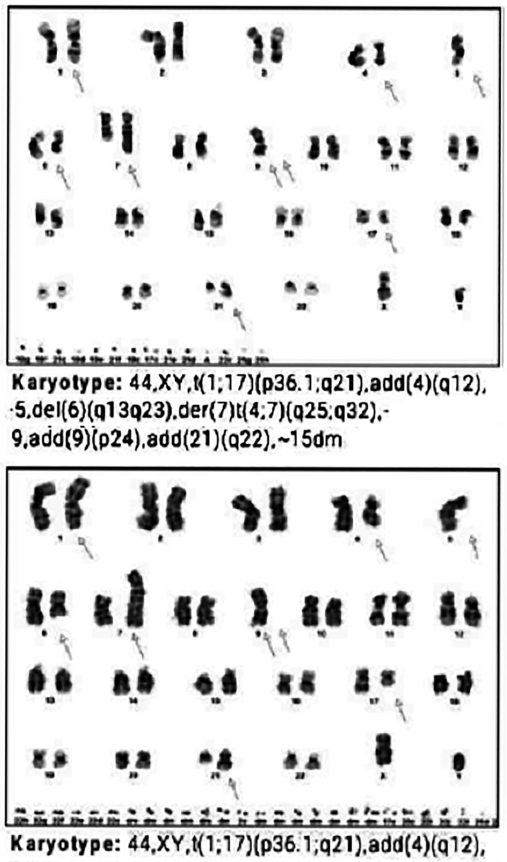


**Figure 2: Bone marrow Karyotype.**

## DISCUSSION

APL is a subtype of AML and comprises around 5-8% cases of AML.[6,7] APL was first described as a hyper-acute fatal illness associated with a haemorrhagic syndrome in the late 1950s in Norway and France. Later, Jean-Bernard described the two most important consequences of APL, *i.e.*, disseminated intravascular coagulation (DIC) and hyperfibrinolysis.[8] By 1973, daunorubicin was used as a successful treatment option for APL. In 1990, various studies offered a link between a translocation between chromosomes 15 and 17 and the pathophysiology of APL, which accounts for around 98% of the cases of APL. Later, ATRA and ATO were added to the treatment regimen of APL, thus targeting the pathogenic oncogene and inducing terminal differentiation of leukaemic promyelocytes. The addition of ATRA and ATO in the treatment of APL transformed it from a highly fatal type of AML to a highly curable form.[9]

The classic form of APL translocation is *PML: RARA* fusion gene, *i.e.*, t(15; 17); however, very rarely APL possesses variant translocations which usually do not harbour *PML* and only have *RARA* as the main culprit, as shown in Table I.[4] Since ATRA and ATO target *PML: RARA* fusion gene, in case of variant translocations, this treatment option may not work effectively, leading to treatment failure and fatal outcomes.

In this case, the child had abnormal promyelocytes with multiple Auer rods on morphology but lacked the classic translocation of APL i.e. *PML: RARA* fusion gene or t(15; 17). In this case, the child had an alteration in chromosome 17 and was initially given a high--risk APL induction regimen, but unfortunately, the child did not respond to it. After a detailed literature review and discussions in MDT meetings, it was recommended to proceed with a high-risk AML protocol. The child achieved both morphological and molecular remission after this treatment. However, due to financial limitations, the family was unable to afford a haplo-identical haematopoietic stem cell transplant. After the second cycle of induction, the child relapsed and, ultimately, passed away.

Various studies have shown that in variant translocations of APL, the response to ATRA is variable (*i.e.*, sensitive to resistance), but there is a constant ATO resistance.[10] As we know, inducing differentiation is just not sufficient in achieving the desired response in APL treatment, but it is mandatory to remove the culprit oncogene.[11]

This is the first case of APL with such a variant translocation reported in Pakistan. As per the literature review, in variant APL translocations, the standard APL protocol may not work; hence, trying upfront AML protocols followed by bone marrow transplants in such cases may help in getting a cure. It is important to document such cases to gather their data, discuss the effectiveness of attempted treatments, and analyse subsequent responses. This ensures that if similar cases arise in the future, relevant treatment data will be readily accessible.

**PATIENT'S CONSENT:**
An informed consent was obtained from the parents of the patient.

**COMPETING INTEREST:**
The authors declared no conflict of interest.

**AUTHORS' CONTRIBUTION:**
SB: Contributions to the conception, drafting, design, and interpretation.
IAS, SS: Analysis and interpretation of data for the work and revision of the manuscript critically for important intellectual content.
AHA: Revision of the manuscript critically for important intellectual content.
All authors approved the final version of the manuscript to be published.

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