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CASE REPORT

Tetraploid/near-tetraploid acute promyelocytic leukaemia with double (15;17) translocation

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Abstract

A 57-year-old man presented with intermittent fever and bleeding following dental surgery. Peripheral smear and bone marrow aspirate exhibited unusually large and bizarre-looking abnormal cells which were found to be myeloblasts with aberrant CD56 and CD2 expression on immunophenotyping. Fluorescence in situ hybridization analysis revealed an extra *RARA* gene rearrangement. This finding correlated well with a near-tetraploid karyotype with double t(15;17)(q22;q21). Bcr-3 type *PML/RARA* copies were identified in reverse transcriptase-polymerase chain reaction. The diagnosis of near-tetraploid acute promyelocytic leukaemia (APML) was established. The patient was treated with all-trans retinoic acid and idarubicin and six weeks later achieved complete remission. Tetraploid/near-tetraploid APML is exceedingly rare. It is a distinct cytogenetic subgroup with unique clinical and biological features as highlighted by atypical morphology, frequent CD2 expression and association with the bcr-3 type *PML/RARA* fusion transcripts. Early recognition of this rare entity is essential for timely and appropriate treatment.

Keywords: tetraploidy/near-tetraploidy, acute promyelocytic leukaemia, double t(15;17), bcr-3 type *PML/RARA*

INTRODUCTION

Acute promyelocytic leukaemia (APML) is a subtype of acute myeloid leukaemia (AML) with distinctive clinicopathological features, often presenting with severe coagulopathy. Morphologically, it is identified by its bilobed or dumb-bell-shaped nuclei and frequent occurrence of Auer rods. APML is characterised by a balanced reciprocal translocation between chromosomes 15 and 17 resulting in the fusion of the retinoic acid receptor alpha (*RARA*) and promyelocytic leukaemia (*PML*) genes.[1] As in other subtypes of AML, most chromosomal abnormalities in APML are diploid. APML showing tetraploidy or near-tetraploidy (T/NT) (81-103 chromosomes) is very rare.[2] In a ten-year observational study in China, T/NT was detected in only 5 out of 660 APML cases (0.75%).[3] The mechanism of tetraploidy development is uncertain. However, T/NT may indicate clonal evolution and secondary change in AML.[4] In this report, we describe a rare case of tetraploid/near-tetraploid APML with double (15;17) translocation.

CASE REPORT

A 57-year-old Indian man, with diabetes mellitus, presented with intermittent fever for about a month and excessive bleeding following dental surgery for 2 days before admission. Physical examination revealed extensive ecchymosis at the insulin injection and venepuncture sites on his limbs and abdomen. No organomegaly was detected on abdominal examination. His coagulation profile was abnormal with prolonged prothrombin time of 17.7 seconds (reference range 9.4 - 12.6 seconds) and low fibrinogen level of 1.01g/L (reference range 1.89 - 4.14g/L). Full blood count and peripheral blood smear showed haemoglobin of 85g/L, white cell count of 5.3 x 10^9/L and platelet count of 6 x 10^9/L with a leucoerythroblastic picture and 10% circulating blasts.

The bone marrow aspirate was hypercellular with 55% atypical blast cells. There were many bizarre-looking and unusually large blasts. Some

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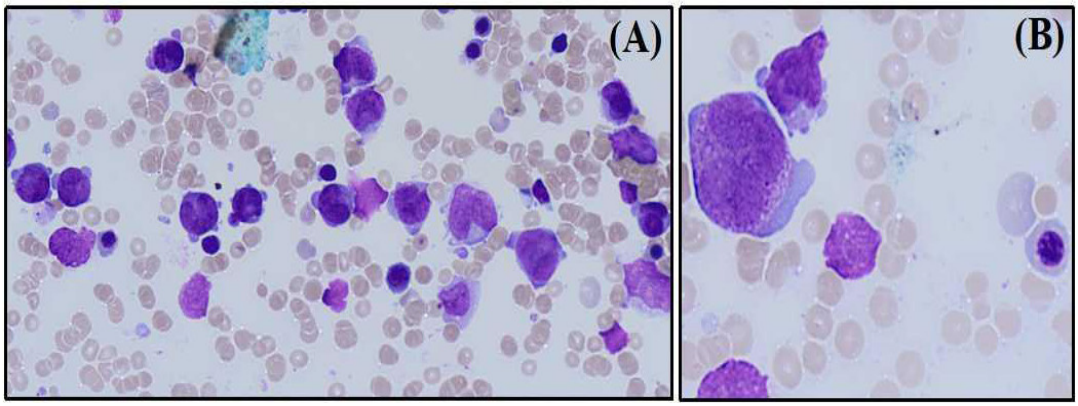

FIG. 1: (A&B) Bone marrow aspirate exhibiting unusually large and bizarre-looking blast cells with some showing cytoplasmic blebs [May-Grunwald Giemsa stain, x40 (A) & x100 (B)].

of these blasts displayed folded or lobulated nuclei with cytoplasmic granules as well as cytoplasmic blebs. No Auer rods or faggot cells were detected (Fig. 1). In flow-cytometry analysis, leukaemic cells were positive for CD13, CD33, CD117, cMPO, CD34 (heterogenous), CD64, CD56 and CD2 but were negative for HLA-DR, CD11b, CD15, CD14, CD41, CD61, CD71 and glycophorin (Fig. 2). Although the leukaemic cells did not show characteristic morphology of APML, the bleeding diathesis and some distinctive immunophenotypic features such as lack of expression of HLA-DR and granulocytic maturation markers (eg. CD11b) warranted urgent fluorescence in situ hybridisation (FISH) analysis to exclude this possibility.

Interphase FISH on a direct marrow aspirate smear using RARA break-apart probes (Cytocell, Cambridge, United Kingdom) showed the unusual finding of two abnormal break-apart signals suggesting the presence of an extra *RARA* gene rearrangement and two normal fusion signals indicating the presence of extra chromosome 17. These changes were detected in 55% (110/200) of interphase nuclei examined (Fig. 3) and confirmed the diagnosis of APML. Features noted in FISH test correlated well with conventional cytogenetic analysis which exhibited an abnormal clone with near-tetraploid

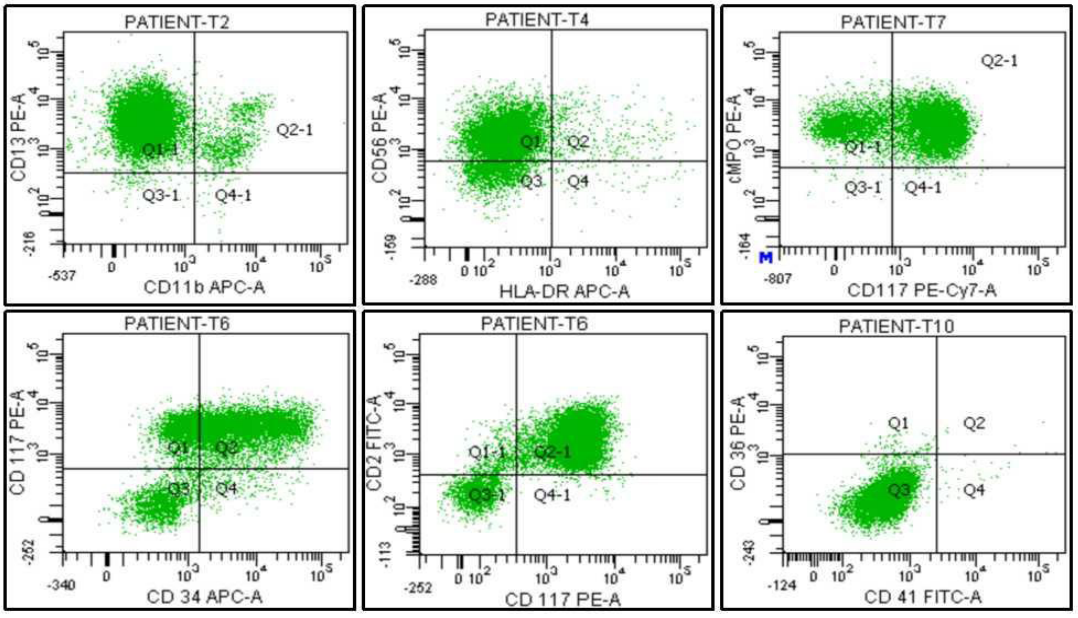

FIG. 2: Flow cytometric analysis of bone marrow aspirate showing leukaemic cells are CD13(+), CD56(+), cytoplasmic MPO(+), CD117(+), CD34(+), CD2(+), CD11b(-), HLA-DR(-), CD36(-) and, CD41(-).

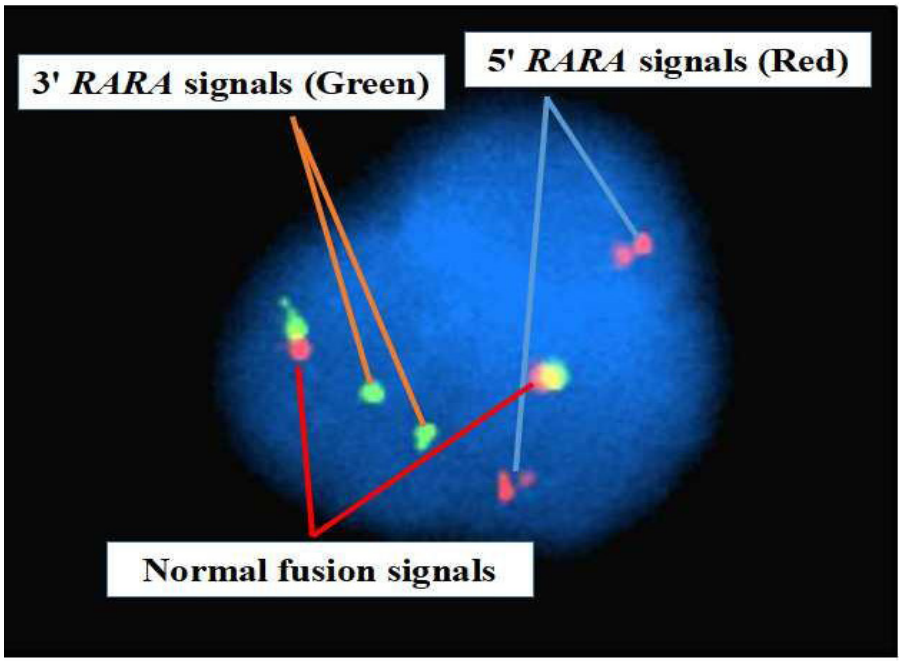

FIG. 3: FISH analysis using RARα break-apart probes on interphase nuclei showing abnormal break-apart signals (separate red and green signals) and normal fusion (red/green) signals in 110 out of 200 cells examined.

karyotype and double t(15;17)(q22;q21). His karyotype was reported as 89~92,XXYY,t(15;17)(q22;q21)x2[7]/46,XY[5], according to the criteria of ISCN 2016 (Fig. 4). Bcr-3 type *PML/RARA* copies were identified by a reverse transcriptase-polymerase chain reaction (RT-PCR). Following FISH results, an induction therapy, consisting of oral all-trans retinoic acid (ATRA) 45mg/m^2/day for 8 weeks with intravenous idarubicin 12mg/m^2 on day 1, day 3 and day 5, was started promptly. The patient's initial treatment phase was complicated by

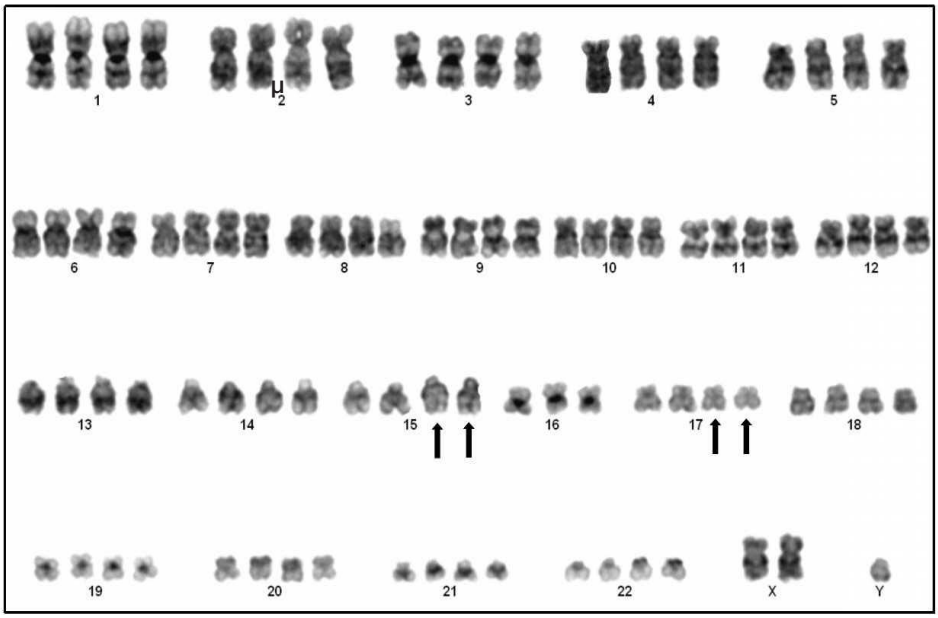

FIG. 4: G-banded karyotypes of bone marrow cells: 89~92,XXYY,t(15;17)(q22;q21)x2 [Arrows indicate derivative chromosomes 15 and 17]

neutropenic sepsis, severe pneumonia, and acute renal failure. However, he attained complete morphological and molecular remission 6 weeks after induction chemotherapy. He then underwent three cycles of consolidation therapy with intravenous idarubicin. Repeat bone marrow examination and molecular analysis after completion of consolidation treatment showed the patient remained in morphological and molecular remission. The latest molecular analysis which was done 20 weeks after consolidation therapy revealed undetectable *PML-RARα* fusion copies. Currently, the patient was undergoing maintenance therapy with ATRA, 6-mercaptopurine and weekly methotrexate.

DISCUSSION

Tetraploidy or near-tetraploidy is a rare chromosomal abnormality in acute myeloid leukaemia (AML) and is generally associated with poor prognosis.[5] In APML, T/NT is even rarer, with only 15 cases reported in the literature.[3,4,6-12] The majority of the patients reported were males of Asian origin.[2,4] In keeping with previous reports, our case revealed certain unique morphological features such as unusually large and bizarre-looking blast cells, and the infrequent occurrence of Auer rods and faggot cells.[2,3,10] The presented case also showed aberrant expression of CD2 expression and bcr-3 type PML/RARα fusion transcripts in RT-PCR as previously documented in such T/NT APML cases.[2,3,4,7,10,11] In contrast to almost every other disease for which treatment is started only after the correct diagnosis is fully established, treatment must begin before the diagnosis is confirmed in patients with suspected APML.[13] A presumptive diagnosis of APML is usually made on the morphology of the peripheral blood smear and/or bone marrow aspirate. Given the potentially rapidly fatal haemorrhagic diathesis so characteristic of APML, the early recognition of this rare entity of APML with unusual morphology is very important to provide timely and appropriate treatment.

APML with T/NT karyotype is a distinct cytogenetic subgroup with unique clinical and biological features. Based on the previous reports, APML with T/NT appears to have a similar clinical outcome to diploid APML and this suggests that t(15;17) is still the main driver of prognosis in APML patients.[2,3] Our patient has shown a good initial response to ATRA and chemotherapy, and he continues to be in complete molecular remission at 16 months from the initial diagnosis. Nevertheless, it is difficult to draw a firm conclusion in regards to the long-term prognosis of APML patients with a T/NT karyotype due to the very small number of such cases reported. It will be necessary to study more such cases in order to understand this rare cytogenetic subgroup better.

REFERENCES

1. Wang Z-Y, Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood. 2008; 111: 2505-15.
2. Dalia SM, Horna P, Zhang L. Tetraploidy acute promyelocytic leukemia with double t(15;17)/PML-RARA, a case report with review of literature. Int J Clin Exp Pathol. 2014; 7(8): 5363-8.
3. Pan J, Xue Y, Qiu H, Wu Y, Wang Y, Zhang J, Shen J. Tetraploid clone characterized by two t(15;17) in five cases of acute promyelocytic leukemia. Cancer Genet Cytogenet. 2009; 188: 57-9.
4. Oh SH, Park TS, Kim HH, Chang CL, Lee EY, Son HC, Chung JS, Cho GJ. Tetraploid acute promyelocytic leukemia with double t(15;17) and PML/RARA rearrangements detected by fluorescence in situ hybridization analysis. Cancer Genet Cytogenet. 2003; 145: 49-53.
5. Huang L, Wang SA, Dinardo C, *et al*. Tetraploidy/near-tetraploidy acute myeloid leukemia. Leukemia Research. 2017; 53: 20-7.
6. Au WY, Ma SK, Lam CC, Chan LC, Kwong YL. Tetraploid acute promyelocytic leukemia with large bizarre blast cell morphology. Cancer Genet Cytogenet. 1999; 115: 52-5.
7. Kaito K, Otsubo H, Dobashi N, Usui N, Kobayashi M. CD2+ tetraploid acute promyelocytic leukemia variant with double (15;17) translocations. Int J Hematol. 2005; 81: 29-31.
8. Kojima K, Imaoka M, Noguchi T, Narumi H, Uchida N, Sakai I, Yasukawa M, Fujita S. Hypocellular acute promyelocytic leukemia with a tetraploid clone characterized by two t(15;17). Cancer Genet Cytogenet. 2003; 145: 169-71.
9. Kuyama J, Tsumori Y, Aoyama K, Kosugi S, Take H, Matsuyama T. Tetraploid acute promyelocytic leukemia with double PML/RARA gene rearrangements successfully treated with all-trans retinoic acid. Int J Hematol. 2004; 79: 405-6.
10. Mohamed M and Dun K. Tetraploidy with double t(15;17)(q22;q21) in acute promyelocytic leukaemia. Pathology. 2013; 45: 203-5.
11. Morita Y, Takahashi A, Yamamoto K, Miki T, Murakami N, Miura O. Secondary near-tetraploidy with double der(15)t(15;17) in acute promyelocytic leukemia in relapse. Cancer Genet Cytogenet. 2004; 149: 131-6.
12. Ravella PM, Liu D, Kojima K, Weisberger J, Miura O, Kuyama J, Au W, Seiter K. Acute promyelocytic leukemia with tetraploid karyotype: first report in the Western hemisphere and update of previous reports. Leuk Res. 2011; 35: e93-5.
13. Tallman MS, Altman JK. How I treat acute promyelocytic leukemia. Blood. 2009; 114: 5126-5.