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Case Report

Tetraploidy acute promyelocytic leuemia with double t(15;17)/*PML-RARA*, a case report with review of literature

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Abstract: Acute promyelocytic leukemia (APL) with tetraploidy chromosome harboring t(15;17)(q23;a21) is extremely rare. To date, there are 14 such cases reports that describe this entity, mostly found in Eastern hemisphere. Herein we described a 51-year-old man with a diagnosis of tetraploid acute promyelocytic leukemia with double (15;17) translocations and compare the prototypically clinicopathologic, genetic and molecular findings with those reported in the literature.

Keywords: Acute promyelocytic leukemia, tetraploid, *PML-RARA*, All trans-retinoic acid (ATRA), leukemia

Introduction

Classic acute promyelocytic leukemia (APL) is a form of acute myeloid leukemia with a unique translocation (15;17)(q22;q21), the fusion transcript with the promyelocytic leukemia *(PML)* gene and the retinoic acid receptor α (*RARA*). Clinically, without an early diagnosis it can be associated with fatal hemorrhage due to disseminated intravascular coagulopathy (DIC). Patients with suspected APL should be started on all-trans retinoic acid (ATRA) immediately which helps lessen the development of DIC. ATRA has been shown to be highly effective for inducing complete remission and cure with or without the combination with other agents [1]. To date, with a standard protocol consisting of ATRA and anthracycline based chemotherapy, a 10-year survival has been reached by 77% of APL patients [2]. Pathologically, APL can be divided into two morphologic variants: hypergranular versus microgranular. In the hypergranular form, the leukemic blasts resemble normal promyelocytes but are heavily loaded with azurophilic cytoplasmic granules, which frequently are accompanied by single to numerous Auer rods. Distinguishing it from the classic, hypergranular variant of APL, the microgranular form shows oval to often "cup-shaped", concave or convoluted nuclei with some to inconspicuous cytoplasmic granules and rare Auer rods [3].

Similar to the other subtypes of acute myeloid leukemia, most chromosomal abnormalities in APL are diploid [3]. APL showing tetraploidy in adults is very rare with 14 cases reported [4-13]. To our knowledge, our case is the first to report tetraploid APL in an adult of Caribbean origin. Previous cases highlight individuals from China, Japan, Korea, Australia, Greece, and of Eastern European decent living in the United States. We report our case and review the 14 other cases to highlight clinicopathologic findings in tetraploid APL.

Clinical presentation

A 51 year old Caucasian male from the Dominican Republic with a history of uncontrolled diabetes mellitus had routine blood work that showed a WBC count of 1.68 × 10^9/L, absolute neutrophil count (ANC) of 0.52 × 10^9/L, hemoglobin of 148 g/L, and platelet

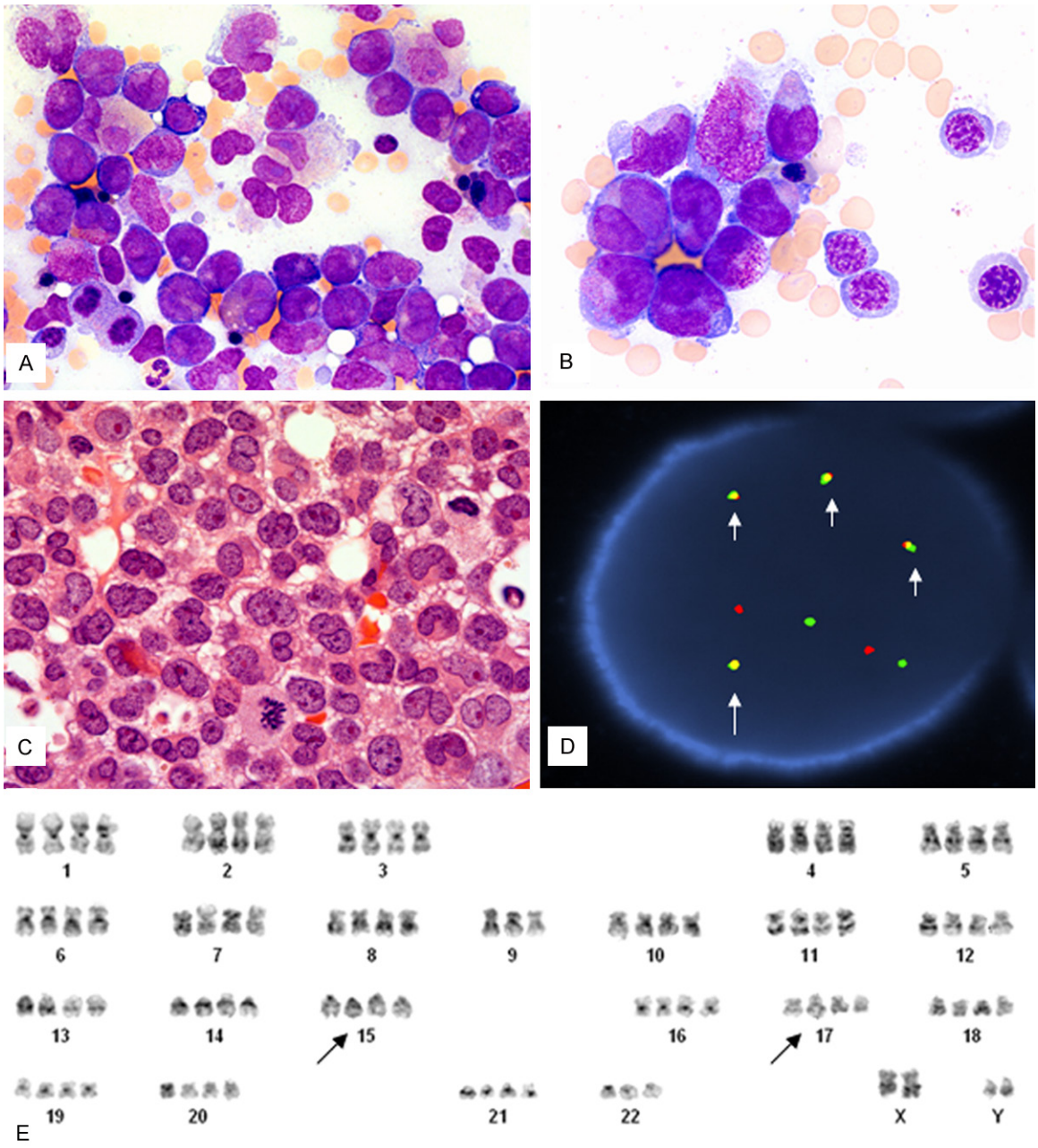

Figure 1. Classic Morphologic Characteristics and Cytogenetic Aberrations of Tetraploid Acute Promyelocytic Leukemia. A. Bone marrow aspirate containing a predominant population of giant immature precursors/promyelocytes, approximately 4-fold size of normal mature lymphocytes, with hypercromatic, concaved or lobulated/irregular nuclei, immature chromatin, variable cytoplasmic azurophilic granules and certain amount of cytoplasm in a background of several smudged nuclei. Active mitosis is also evident (Wright-Giemsa, magnification ×600). B. High power view of a group of bizarre, multilobated blasts with fewer cytoplasmic granules associated with several normoblasts (Wright-Giemsa, magnification ×1000). C. The bone marrow core biopsy was diffusely replaced by sheets of blasts/promyelocytes. The normal hematopoietic elements are diminished (Hematoxylin and Eosin, ×1000). D. FISH study using Vysis LSI PML/RARA dual color, dual fusion translocation probes, 15q22 LSI PML (SpectrumOrange) and 17q21.1 LSI RARA (SpectrumGreen) probes, detected four pairs of fusion signals (yellow, white arrows indicated), in addition to two green and two red normal signals (2G2R4F) in 196 of 200 cells. E. Conventional G-banding revealed abnormal male karyotype: 91,XXYY,-9,t(15;17)(q24;q21.1)x2[cp20] (The arrows indicate abnormal chromosome at long arms).

Table 1. Pathologic and molecular characteristics of tetraploidy APL and clinical outcome

Case/Reference.	Age/Sex	Country	Immunophenotype	Cytogenetics	Initial Treatment	Outcome
1, Kaito et al.	56/M	Japan	CD2+, CD13+, CD33+, CD34+, CD56+, HLA-DR-	92,XXYY,t(15;17)(q22;q21)x2	ATRA	Died at 5 days
2, Oh et al.	50/F	South Korea	CD2+, CD13+, CD33+, CD34-, CD56-, HLA-DR-	92,XXXX,t(15;17)(q22;q21)x2[20]	ATRA, daunorubicin, cytarabine	Died at 16 days
3, Morita et al. *(at relapse)	50/M	Japan	CD2+, CD13+, CD33+, CD34+, HLA-DR+	45,XY,add(1)(p36),-9,der(15)t(15;17),-17,add(20)(q13),-21,+mar1,+mar2[2]/46,idem,+mar3[6]/45,idem,del(11)(p11),add(13)(p11),+18,+21,-mar1,-mar2[2]/86,XX,-Y,-Y,add(6)(p21)×2,-8,-9,-11,-12,der(15)t(15;17)×2,-16,-17,-17,+18,-19,+mar4,+mar5[2]/46,XY[5]	ATRA	Died 80 months from diagnosis after multiple treatments
4, Mohamed et al.	32/M	Australia	CD13+, CD33+, CD34-, CD117+, HLA-DR-	92,XXXX,t(15;17)(q22;q21)x2	ATRA and chemotherapy	CR at 12 months
5, Ravella et al.	48/M	United States (Eastern European decent)	CD2-, CD13+, CD33+, CD34-, CD56-, CD117-, HLA-DR-	92,XXYY,t(15;17)(q22;q21)X2[4]/92,XXYY,add(5)(q22),t(15;17)(q22;q21)X2[18]/46,XY[13].	ATRA, idarubicin, cytarabine x 3	CR at 8 months
6, Pan et al.	21/M	China	CD2+, CD13+, CD33+, CD117+	46,XY,t(15;17)[18]/92,XXYY,t(15;17)x2[6]/j46,XY[1]	ATO	CR at 6+ months
7, Pan et al.	26/M	China	CD2+, CD13+, CD33+	92,XXYY,t(15;17)x2[10]	ATRA+ATO	CR 2.5+ months
8, Pan et al.	68/M	China	CD2+, CD13+, CD33+, MPO+	92,XXYY,t(15;17)x2[5]/j46,XY[5]	ATRA+ATO	CR 12+ months
9, Pan et al.	40/M	China	CD13+, CD33+	92,XXYY,t(15;17)x2[10]	ATRA	CR 40+ months
10, Pan et al.	38/M	China	CD33+	92,XXYY,t(15;17)x2[18]/46,xy[2]	ATRA	CR 120+ months
11, Au et al.	24/M	China	CD2+, CD13+, CD33+, MPO+	73~89,XXY,-Y[18],-3[10],-5[9],-7[4],-9[7],-11[9],-14[10],-15[9],t(15;17)[10],t(15;17)[4],der(15)t(15;17)[4],-17[8],-18[7],-19[9],-20[18],+mar1[9],+mar2×2[10],+mar3[7][cp10]/46,XY[6]	ATRA then daunorubicin+ cytarabine	CR 11+ years
12, Kojima et al.	53/M	Japan	NA	92,XXYY,del(2)(q?),t(15;17)(q22;21)x2[4]/46,XY[16]	JALSG-APL97	CR at 96+ months
13, Kuyama et al.	56/M	Japan	CD2-, CD13+, CD33+, CD34-, CD56-, HLA-DR	90[1/6]/91[1/6]/92,XXYY,t(15;17)(q22;q12)×2,-16,-16,+2mar[4/6]	JALSG-APL97	CR at 101+ months
14, Matsouka et al.	49/M	Greece	CD13+, CD33+, CD34+, CD38+, CD56+, HLA-DR-	92,XXYY	ATRA+idarubicin	CR at 2+ months
15, Current Case.	51/M	United States (Caribbean descent)	CD7-, CD13+, CD33+, CD34+, CD56+, CD117+, MPO+, HLA-DR-	91,XXYY,-9,(15;17)(q24;q21.1)x2	ATRA+idarubicin	CR At 33+ months

APL: Acute promyelocytic leukemia; ATRA: all transretinoic acid; ATO: arsenic trioxide; JALSG: Japanese Adult Leukemia Study Group; CR: Complete Remission.

count of 111×10^9/L and was referred to hematology. Hepatitis, HIV, and computed tomography of the chest to pelvis were normal. Bone marrow biopsy demonstrated 95% cellularity completely replaced by sheets of large to giant blasts with promyelocytic or bizarre morphology (**Figure 1A-C**) Flow cytometry study demonstrated these cells to be phenotypically positive for CD45, CD13, CD33, myeloperoxidase (MPO), CD117, and partial CD34 and negative for HLA-DR. Fluorescence in situ hybridization (FISH) revealed 94% of nuclei positive for the promyelocytic leukemia and retinoic acid receptor alpha (PML-RARA x4) fusion signals (**Figure 1D**). Cytogenetics revealed t(15;17)(q24;q21.1) x2 in all 20 metaphases (**Figure 1E**). Findings were consistent with acute promyelocytic leukemia (APL), tetraploidy variant. Induction therapy with all trans-retinoic acid (ATRA) and idarubicin were completed with no complications and post induction bone marrow biopsy revealed 40% cellularity and moderate myeloid hypoplasia. Cytogenetics revealed a normal male karyotype and FISH and PCR studies showed no undetectable PML/RARA fusion products, consistent with APL in molecular remission. The patient achieved a complete remission in 2 months and completed consolidation therapy with ATRA, iadrubicin plus mitraxontrate with 33 months of follow up. He is now on ATRA maintenance without any signs of recurrent disease.

Discussion

The frequency of additional chromosomal abnormalities (trisomy 8, trisomy 21) in APL is around 30%, but their prognostic significance remains unclear since treatment outcomes do not seem difference [14]. Tetraploidy is a rare chromosomal abnormality in acute myelocytic leukemia (AML) and usually conveys a poor prognosis [4, 15]. In APL tetraploidy is even rarer in adults with 14 cases reported in the literature and an incidence rate of 0.75% (n=5) in a ten year period in one center treating 660 APL patients [4-12]. In reviewing the 14 cases reported in the literature the majority of cases are of Asian origin with six cases reported in China, four in Japan, one in Korea, one in Australia, one from Greece, and one of Eastern European descent from the United States. While our case is the second from a patient in the United States, it is the first to report tetraploidy APL from the Caribbean. The significance of an Asian predominance of cases of tetraploidy APL is unclear and may represent a publication bias. The median age of all reported cases is 49 years and there is a male predominance with only one case being female. CD13 and CD33 are consistent findings on flow cytometry of all the cases while there was variable expression of CD117, CD34, MPO, and HLA-DR. Durable complete remissions were seen in 87% (13 of 15 cases) with ATRA based therapy. Not uncommonly, a subset of tetraploidy APL also aberrantly expressed CD2. Two cases died during induction therapy while only one case had died after multiple relapses after 80 months post diagnosis. **Table 1** summarizes the 15 cases of tetraploidy APL.

Similar to diploidy APL, tetraploidy APL had its unique features distinguishing it from the other type of AML. When compared with conventional APL, the promyelocytes from tetraploidy APL are uniformly larger to giant in size and contain "bizarre" shaped nuclei. The neoplastic cells contain either hypergranulated or microgranulated cytoplasm which is similar to other cases of APL. Auer rods or "Faggot" cells are infrequently noted in APL with tetraploidy. Many such cases displayed "cup-shaped" or convoluted nuclei, which could mimic a variant of acute myeloid leukemia with "cup-shaped" nuclei or acute monocytic leukemia [16]. The latter is often associated with NPM mutation or FLT/ITD mutation [16]. Common genetic mutations such as the FLT3-ITD mutation which is a poor prognostic factor for AML continue to not impact survival in APL with an analysis of 245 APL cases showing 31% with FLT/ITD mutation but with no significant impact on overall survival [17]. Although none of the tetraploidy cases were tested for their FLT/ITD status it is likely that this would not impact survival in tetraploidy APL. As highlighted by the case described by Matsouka et al, cytogenetic analysis or FISH may miss t(15;17) in rare cases and thus we recommend that PCR testing for the PML/RARA gene rearrangement be done in all suspected cases of APL in order to initiate ATRA based therapy quickly [13].

Our analysis of the 15 cases of adult tetraploid APL highlights that the prognosis remains favorable with 13 of 15 patients obtaining a complete remission with ATRA based induction therapy. This is different from outcomes seen in other tetraploid AML beyond APL in which one

series of 25 patients continues to show poor prognosis in these patients [15]. It seems that t(15;17) remains the driver genetic aberration in patients with tetraploid APL and targeted treatment with ATRA based therapy produces favorable clinical results. Due to the variability of treatments in the reported cases no further conclusions can be made as to which combination therapy has improved outcomes in tetraloidy APL.

In conclusion, we report the first case of tetraploid APL from a patient from the Caribbean and only the second from the Western hemisphere. The significance of geographic distribution of the sub-entity is unclear. The review of the cases suggests that tretraploid APL is a disease with a median age of 49 and has a male predominance. Morphologically and immunophenotypically cases of tetraploidy APL are similar to those with diploid karyotypes. The outcomes in patients with tetraploidy APL are similar to diploidy APL and these cases suggest that the t(15;17) is the main driver of prognosis in patients with APL and with ATRA based therapy outcomes remain favorable. Since t(15;17) can be absent on cytogenetic analysis or FISH we also recommend that all patients with suspected APL have the PML/RARA PCR completed to confirm the diagnosis. We encourage others to report cases of tetraploidy APL and are pursuing a genetic profiling study in order to better understand this rare variant of APL.

Disclosure of conflict of interest

None.

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