



A rare case of acute myeloid leukemia with der(1)t(1;19)(p13;p13.1)

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ARTICLE INFO

Keywords:

Acute myeloid leukemia
AML
RUNX1
Hand-mirror blasts
t(1;19)

ABSTRACT

We present a case of acute myeloid leukemia with der(1)t(1;19)(p13;p13.1) translocation and *RUNX1* mutation. A literature review summarizing the clinical, pathological, and molecular features of the published cases is also presented.

1. Introduction

Cytogenetic abnormalities provide important prognostic information and serve as the frame work for risk adapted therapy for acute myeloid leukemia [1]. Some of the karyotypic abnormalities are sufficiently common, have been well characterized at the molecular level, and are known to describe distinct entities. For example translocations t(8;21), t(15;17), and t(16;16) are known to impart a favorable prognosis while abnormalities of chromosome 3q, monosomies of chromosome 5 and/or 7, or complex karyotypes portend an adverse prognosis [2,3].

Up to 10% of AML patients have rare recurrent cytogenetic abnormalities [4]. Many of these have not been characterized in detail and their impact on prognosis remains unclear. We present a case of AML with der(1)t(1;19)(p13;p13.1) as the sole cytogenetic abnormality along with a concise review of the 4 previously described cases of AML with this anomaly. Next generation sequencing performed in our patient at the time of disease relapse identified a *RUNX1* mutation, which has not been described in any of the previously published cases.

2. Case report

A 20-year-old Hispanic male presented with oral ulcers, fever, fatigue and headache. Prior to presenting to the emergency department, he had received a course of antibiotics for suspected sinusitis. He had developed a pruritic drug rash over his legs, buttocks and abdomen following the antibiotic use. His medical history was significant for

Henoch Schoenlein purpura as a child and mild autism. No familiar history of hematologic diseases reported by the patient or otherwise documented. On examination, temperature was 38.1 °C and heart rate was 125 beats per minute. Blood pressure and respirations were normal. His physical examination showed some non-tender sub-mandibular lymphadenopathy, left upper quadrant tenderness, and a mild maculopapular rash was seen over both legs and lower abdomen. Liver and spleen were not palpable.

Initial laboratory studies showed a leukocyte count of $0.85 \times 10^3/\mu\text{L}$, a hemoglobin of 5.6 g/dL, and a platelet count of $123 \times 10^3/\mu\text{L}$. Leukocyte differential included 2% neutrophils, 3% bands, 13% monocytes, 70% lymphocytes, and 12% blasts. Liver and renal functions were normal.

A bone marrow biopsy showed a cellularity of 70–80% with diffuse infiltration by blasts and suppression of normal hematopoiesis (Fig. 1). Blasts showed monocytic features with a variable proportion of the cells displaying “hand-mirror” morphology with pronounced cytoplasmic tails and blebs (Fig. 2). Flow cytometry revealed the blasts to be CD117(+), CD34(-), HLA-DR(+), CD4 (+) and CD64(+).

Cytogenetic analysis was performed on bone marrow aspirate. All 22 metaphases analyzed revealed the presence of a derivative chromosome 1 resulting from an unbalanced translocation of the short arm of chromosome 19 proximal to 19p13 to the short arm of chromosome 1 at band 1p13: 46, XY, der(1)t(1;19)(p13;p13.1)[22] (Fig. 3).

FISH (Fluorescent in-situ hybridization) analysis was performed using acute leukemia-specific probes. FISH results using the *E2A/PBX1* Translocation, Dual Fusion Probe showed the translocation resulted in

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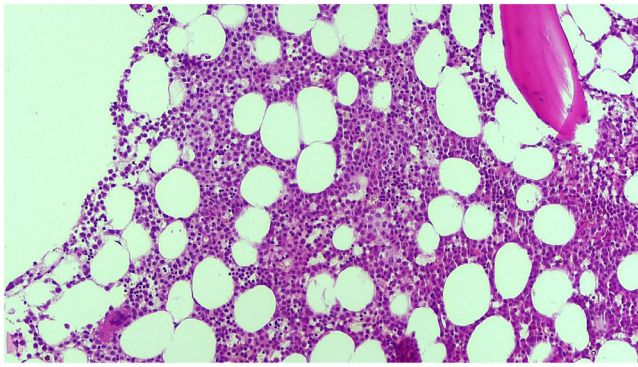


Fig. 1. Bone marrow morphology demonstrating hypercellularity (70–80%) with infiltration of myeloid blasts and suppression of normal hematopoiesis.

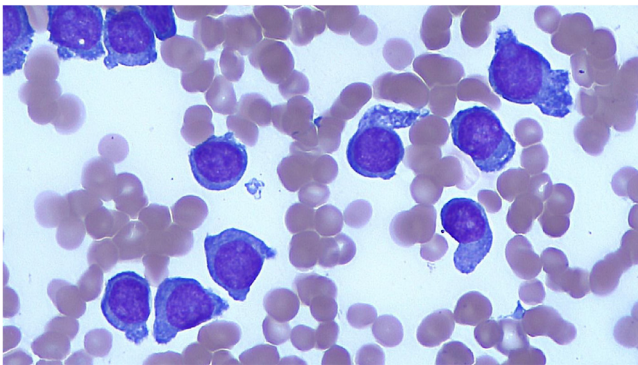


Fig. 2. Myeloid blasts with pronounced cytoplasmic tails (hand-mirror blasts).

an extra copy of the *E2A* gene (19p13.3) on the derivative chromosome (Fig. 4). The *E2A* probe, labelled in green, contains two probes (110 kb and 146 kb) that cover the 3' end of the *E2A* (*TCF3*) gene and flanking region and a 321 kb probe that covers a region 5' (centromeric) to the gene. The *PBX1* probe, labelled in red, contains two probes (147 kb and 110 kb) that map within the *PBX1* gene and a 117 kb probe that maps 3' (telomeric) to the gene. In a normal cell, two red and two green signals (2R, 2G) should be visible. Due to the close proximity of the green

signals, these two signals may overlap and appear as one signal in a small proportion of cells. In this case, since there is gain of an extra *E2A* gene due to the unbalanced translocation, 2R3G signal pattern was evident by FISH (Fig. 4). DAPI images of the metaphases revealed that this extra *E2A* gene copy was on the short arm of chromosome 1 at band 1p13 (Fig. 4). In addition, an extra copy of the *MLL* (11q23.3) gene was also identified (Fig. 5).

Molecular testing at diagnosis with FISH using extended pediatric acute lymphoblastic leukemia panels did not show mutations in *FLT3* (either *ITD* or *TKD*), *NPM1*, *CEBPA* or *KIT*.

The patient underwent induction therapy with a typical 7 + 3 regimen (employing 200 mg/m²/day of cytarabine and 12 mg/m² of idarubicin). Complete remission (by morphology, flow cytometry and FISH) was achieved after induction. Repeat karyotype was 46,XY[20]. The patient was advised to undergo an allogeneic stem cell transplant in 1st remission. He, however, declined and received 4 cycles of consolidation with high dose cytarabine. At the end of 4 cycles of consolidation, a repeat bone marrow aspiration and biopsy showed ongoing morphological and cytogenetic remission.

He relapsed 4 months after completing therapy. Bone marrow biopsy and aspirate again showed “hand mirror” myeloblasts with monocytic differentiation and flow cytometry again identified expression of CD 117, CD 4, and CD 64 without CD 34 expression. Cytogenetic findings at relapse, however, continued to show a normal male karyotype (46,XY[20]) and FISH studies looking specifically for *E2A* and *MLL* showed normal copy numbers.

Next generation sequencing was performed using Illumina sequencing technology to identify variants in genes commonly associated with AML (*ASXL1*, *ATM*, *BCOR*, *BCORL1*, *CBL*, *CDKN2B*, *CEBPA*, *CREBP* (*ATF2*), *CSF3R*, *DDX41*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *GATA1*, *GATA2*, *IDH1*, *IDH2*, *IKZF1*, *JAK2*, *KDM6A*, *KIT*, *KRAS*, *MLL*, *MPL*, *NF1*, *NPM1*, *NRAS*, *PHF6*, *PTEN*, *PTPN11*, *RUNX1*, *SETBP1*, *SF3B1*, *SRSF2*, *STAG2*, *STK11*, *TET2*, *TP53*, *U2AF1*, *WT1*, *ZRSR2*). The above genes, except for *MLL*, were tested using a commercial bait-capture next generation sequencing platform. *MLL* was tested by long range PCR which only detected the presence or absence of the partial tandem duplication. This revealed a missense mutation on the *RUNX1* gene, c.127C > T variant ID 463,980, with a frequency of 55%, which resulted in the replacement of proline with serine at codon 43 of the *RUNX1* protein (p.Pro43Ser). No other variants in the above genes were identified.

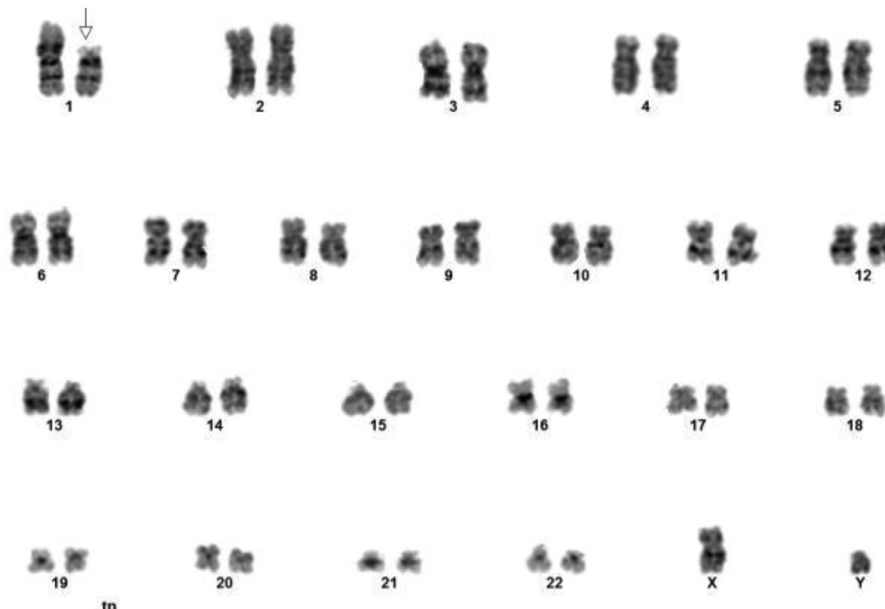


Fig. 3. Cytogenetic analysis demonstrating 46, XY, der(1)t(1;19)(p13;p13.1) karyotype.

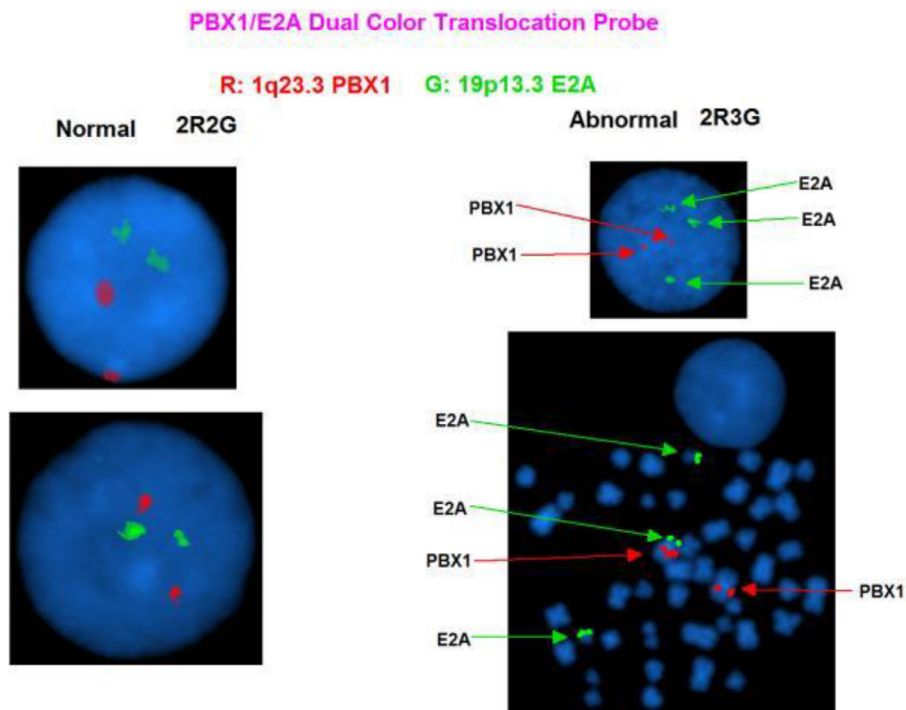


Fig. 4. Fluorescent in situ hybridization demonstrating unbalanced translocation of chromosome 1 band p13 and the short arm of chromosome 19 band p13 resulting in an extra copy of the *E2A* gene.

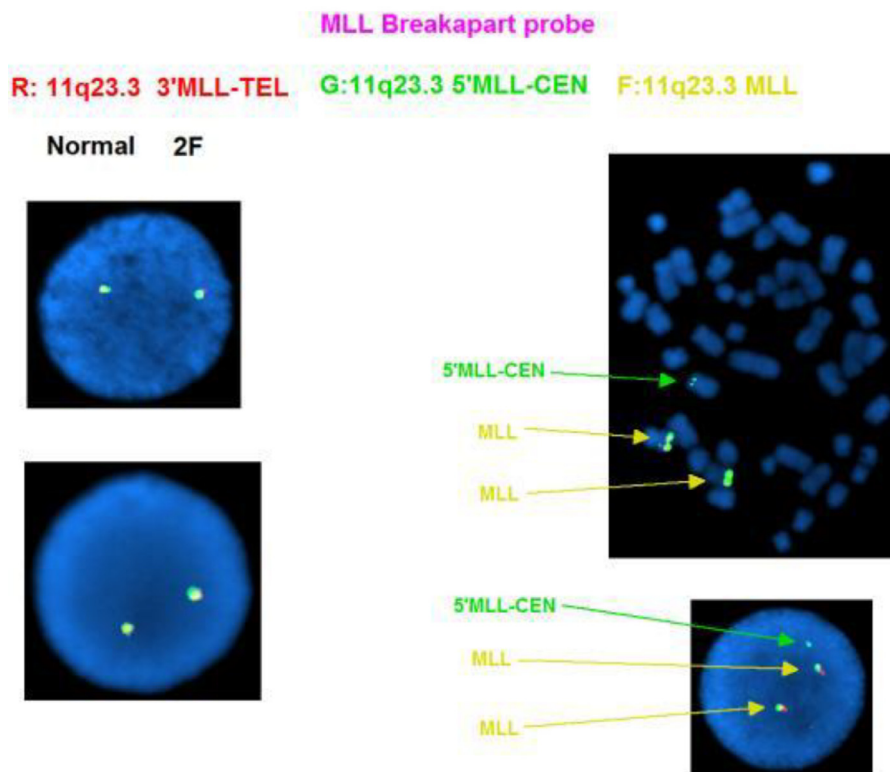


Fig. 5. FISH analysis demonstrating an extra copy of the *5'MLL* (11q23.3) gene.

He received salvage therapy with fludarabine, cytarabine and idarubicin (FLAG-IDA) and was then treated with venetoclax and azacytidine. Second remission lasted 3 months. He then developed leukemia cutis. Repeat therapy with FLAG-IDA was attempted with no response and the patient opted for supportive care alone.

3. Discussion

We present a case of AML with der(1)t(1;19)(p13;p13.1) as the sole cytogenetic abnormality. The Mitelman database for chromosomal aberration and gene fusion, Atlas of genetics and cytogenetics in oncology and hematology, and PubMed were searched for all cases of AML

Table 1
Clinical, pathologic, and molecular characteristics of existing cases demonstrating t(1;19) translocations.

Ref	Age (yrs)	Sex	WBC/(mcl)	Hb (g/dl)	Plt 10 ³ /mcl	Blast morphology	karyotype	Molecular mutations	prognosis
5	36	M	700	5.4	13	M1 with hand mirror blasts.	46,XY, + der(1)(t(1;19)- (p13;p13.1)[cp3]/46,XY	NR	NR
6	1	F	265,000	7	68	M5	47,XX, + der(1)(t(1;19)(p13;p13.1) der(10)inv(10)(p22;5q25)t(10;11)(q25;q25)	NR	CNS relapse at 5 months, expired 8 months.
7	73	M	1100	5	31		48,XY, der(1)(t(1;19)(p13;p13.1), +1 3	IDH2 C419 G > 8 FLT3ITD	Expired, 21 months
7	84	F	10,000	10	56		46,XX, der(1;19)(p13;p13.1), -22	TET2 C4022C > A SF3B1 c.2359 2360delinsT, c.362_363delinsA FLT3ITD	Expired, 1 month
Curr-ent	21	M	850	5.6	123	M5 hand mirror blasts	46, XY,der(1)(t(1;19)(p13;p13.1)	KRAS c.183A > C NPM1 c.859delinsCTCTG RUNX1 p43s	Relapse 9 months.

with der(1)t(1;19). An additional 4 cases of acute myeloid leukemia were identified [5–8]. Table 1 summarizes the clinical, pathological and molecular findings in these, including the current case. The Median age of patients is 36 years (range 1–84). Median presenting WBC count is 1100/mcl (700–265,000). There are 3 males and 2 females. Two patients had M5 blast morphology and two had “hand mirror” blasts noted on smears. In 2 patients der(1)t(1;19) was the sole cytogenetic abnormality, while the other 3 had additional chromosomal abnormalities.

Of the 3 cases where molecular findings were reported (including the current one), 2 had FLT3 ITD mutations; a RUNX1 mutation was found in our case. Our case is unique in being the first to describe the karyotype both at presentation and at relapse and being the first to identify the presence of RUNX1 mutation in association with this karyotype.

RUNX1 encodes for a transcription factor which is essential for hematopoiesis. Point mutations in RUNX1 in acute leukemia were first described in 1999. It is now evident that these are frequent in acute myeloid leukemia being present in up to 33% of AML with normal karyotype or non-complex chromosomal imbalances. Their presence is an independent adverse prognostic factor [9–11]. The current (2016) revision of WHO classification of myeloid neoplasms includes a provisional entity entitled AML with mutated RUNX1 [12,13]. In our case, the lack of RUNX1 mutational testing performed on the initial sample prevent us from excluding acquisition of the mutation at the time of disease relapse when the presence of the abnormal chromosome clone and derivative chromosome were no longer detected. Although there was no familiar history of leukemic disorders in this patient, in view of his young age and high allele burden (55%), the possibility of a constitutional RUNX1 mutation could not be entirely excluded. We conclude that presence of der(1)t(1;19) in AML marks the presence of adverse molecular mutations and poor prognosis. Molecular findings in future cases need to be studied both at presentation and relapse to better understand the biology of this leukemia and improve outcomes.

Acknowledgment

We would like to thank Weidong Zhou, MD and Michael Van Ness, MD at Quest Diagnostics for their assistance with the next generation sequencing result interpretation.

References

- [1] D. Grimwade, Impact of cytogenetics on clinical outcome in AML, editor. in: J.E. Karp (Ed.), Acute Myelogenous Leukemia, Humana Press, Totowa, NJ, 2007, pp. 177–192.
- [2] K. Mrózek, N.A. Heerema, C.D. Bloomfield, Cytogenetics in acute leukemia, Blood Rev. 18 (2) (2004) 115–136.
- [3] Grimwade D., Hills R.K. Independent prognostic factors for AML outcome. Hematology Hematol. Am. Soc. Hematol. Educ. Program 2009:385–95.
- [4] D. Grimwade, R.K. Hills, A.V. Moorman, et al., Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials, Blood 116 (3) (2010) 354–365.
- [5] “NM_001754.4(RUNX1):C.127C>T (P.Pro43Ser) Variation Report - ClinVar - SCV000638125.2.” National Center for Biotechnology Information, U.S. National Library of Medicine, www.ncbi.nlm.nih.gov/clinvar/variation/463980/.
- [6] S.K. Ma, T.S.K. Wan, L.C. Chan, E.K.W. Chiu, Hand-mirror blasts, AML-M1, and der(1)t(1;19)-(p13;p13.1), Leuk. Res. 24 (2000) 95–96.
- [7] Joëlle Tchinda, et al., Novel Der(1)t(1;19) in two patients with myeloid neoplasias, Cancer Genet. Cytogenet. 133 (1) (2002) 61–65, https://doi.org/10.1016/s0165-4608(01)00505-2.
- [8] R.N. Salgado, J. Menezes, M. Calvente, et al., Myeloid neoplasms with der(1)t(1;19) may constitute a specific entity characterized by a cytogenetic biomarker and gene mutations involved in DNA methylation, Leuk. Lymphoma 55 (11) (2014) 2652–2655.
- [9] E2A/PBX1 Translocation, Dual Fusion Probe Kit insert; CytoCELL; DS230/CE v004. 00/2018-01-31.
- [10] S. Schnittger, F. Dicker, W. Kern, et al., RUNX1 mutations are frequent in de novo AML with noncomplex karyotype and confer an unfavorable prognosis, Blood 117 (8) (2011) 2348–2357.

- [11] J.L. Tang, H.A. Hou, C.Y. Chen, et al., AML1/RUNX1 mutations in 470 adult patients with de novo acute myeloid leukemia: prognostic implication and interaction with other gene alterations, *Blood* 114 (26) (2009) 5352–5361.
- [12] V.I. Gaidzik, L. Bullinger, R.F. Schlenk, et al., RUNX1 mutations in acute myeloid leukemia: results from a comprehensive genetic and clinical analysis from the AML study group, *J. Clin. Oncol.* 29 (10) (2011) 1364–1372.
- [13] D.A. Arber, A. Orazi, R. Hasserjian, et al., The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, *Blood* 127 (20) (2016) 2391–2405.