Acute myeloid leukemia with promyelocytic morphology lacking *RARA* rearrangement and with double minutes, *MYC* deletion and 2 cell lines with amplification of *MYC* region: case report and literature review

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Abstract Acute promyelocytic leukemia (APL) typically demonstrates the translocation t(15;17)(q24;q21) leading to *PML-RARA* fusion in ~92 % of the cases. The remaining t(15;17) negative APL-like cases may have other cytogenomic rearrangements, including cryptic *PML-RARA* fusion, translocation variants, or *MYC* gene amplification. The morphologic and cytogenetic profile of the APL-like cases with *MYC* amplification and the prognostic implications are largely unknown due to rarity of these cases. Here, we present a case of acute myeloid leukemia with promyelocytic morphology lacking the classic t(15;17) and *RARA* rearrangement, with der(5)t(5;17)(q13;21), *MYC* deletion, double minutes, and two cell lines with amplification of the *MYC* region. The two cell lines differed in contribution to the proportion of the cells and copy number of the amplified probes during the clinical course. This is likely the first case with such a complex molecular cytogenetic evolution detailed in the same patient. Literature review revealed that most of the APL-like cases

with *MYC* amplification have no t(15;17) and *PML-RARA* (78.5 %; 7/8 cases) but a complex karyotype (75 %; 6/8 cases). Deletion 17p/monosomy 17 and deletion 9p/monosomy 9 are reported in ~40–50 % of the cases and are associated with poor prognosis. *MYC* amplification alone may not be a reliable prognostic indicator in APL-like cases. Our findings can be very helpful for clinicopathologic/cytogenetic correlation and potentially management of such rare but potentially unrecognized APL-like patients.

Keywords Acute promyelocytic leukemia · Lacking t(15;17) · Lacking *RARA* fusion · FISH · *MYC* deletion · *MYC* amplification

Introduction

Acute promyelocytic leukemia (APL) is characterized by a proliferation of blasts and morphologically abnormal promyelocytes in the bone marrow and peripheral blood. Diagnosis of APL requires demonstration of rearrangements involving *RARA* (17q21). A vast majority (~92 %) of APL cases have the classic translocation t(15;17)(q24;q21) leading to *PML-RARA* fusion [1]. The remaining t(15;17) negative APL cases may have (1) cryptic insertions or other rearrangements leading to *PML-RARA* fusion detectable by FISH, RT-PCR, long-distance DNA-PCR or sequencing analysis; and (2) translocation variants [1–3]. Seven translocation variants have been reported with a fusion of *RARA* to one of the partner genes: *PLZF* (or *ZBTB16*) at 11q23, *NUMA1* at 11q13, *NPM1* at 5q35, *STAT5B* at 17q21, *PRKARIA* at 17q24, *FIP1L1* at 4q12, and *BCOR* at Xp11

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[1, 3]. Patients with *PML-RARA*, *NPM1-RARA*, and *NUMA1-RARA* respond to treatment with all-trans retinoic acid (ATRA), while those with *PLZF-RARA* and *STAT5B-RARA* do not [1, 3, 4]. Other common aberrations in APL include trisomy 8, deletion 9q, and *ider(17)(q10)t(15;17)* [5].

Amplification of *MYC* (8q24) is reported in rare cases of cancer; more often in solid tumors than leukemias. *MYC* amplification can be seen as double minutes (dmin) (e.g., double dots, larger spherical or fragment structures and rings) or homogeneously stained regions [6–8]. Gene amplification in cancers can confer growth advantage to the mutated cells and is often associated with disease progression, drug resistance, and poor prognosis. *MYC* amplification has been reported in seven APL-like cases, and its prognostic significance is not well understood [7–13].

Here, we present a case of acute myeloid leukemia (AML) with promyelocytic morphology lacking the classic *t(15;17)* and *RARA* rearrangement and with *der(5)t(5;17)(q13;21)*, *MYC* deletion, dmin, and two cell lines with amplification of the *MYC* region.

Case report

A 62-year-old woman presented with a recent history of community-acquired pneumonia treated with antibiotics; after which, persistent fatigue and dysgeusia was noted. A complete blood count showed leukocytosis with blasts and promyelocytes in the peripheral blood. On admission, she did not have any active bleeding, and her physical exam was unremarkable. Initial laboratory assessment showed a white blood cell count of $32.3 \times 10^9/L$ (normal 4–10) with elevated blasts at $9.7 \times 10^9/L$ (30 % of total leukocytes). Her hemoglobin was 79 g/L (normal 115–160) with a platelet count of $47 \times 10^9/L$ (normal 150–400). Her INR was 1.0 (normal 0.9–1.1), with a PTT of 29 s (normal 25–37) and a fibrinogen of 4.04 g/L (normal 2–4). Her serum LDH level was markedly elevated at 1,995 u/L (normal ≤ 214) with a urate level of 442 mol/L (normal ≤ 340), a phosphate level of 1.98 mol/L (normal 0.80–1.33), and creatinine of 89 mol/L (normal 55–100). A bone marrow aspirate showed heavy infiltration by a combination of myeloblasts (approximately 30 % of all nucleated cells) and hypergranular promyelocytes (approximately 50 % of all nucleated cells) (Fig. 1). Auer rods were identified but not prominent. Flow cytometric analysis of the bone marrow identified a myeloblast/promyelocyte population representing 80 % of the total nucleated cells; expressing CD33 and CD15; partial expression of CD117, CD11b, CD13, and HLA-DR; dim expression of CD10; and negative expression of CD56, CD16, MY4, and CD34. The morphological and immunophenotypical findings were consistent with AML with promyelocytic morphology. The patient underwent standard induction chemotherapy with 3 + 7 (cytarabine (100 mg/m²) and daunorubicin (180 mg/m²)). After G-banding identification

Fig. 1 Morphological findings in bone marrow showing hypergranular promyelocytes

of absence of the classic *t(15;17)*, but with the translocation *t(5;17)* (see [Molecular cytogenetics results](#)), the patient was started on ATRA 45 mg/m² which she tolerated well until time of discharge. The decision of using ATRA was based on previous reports that APL patients bearing the *t(5;17)* translocation might respond to this drug [14]. On achieving morphological remission and improvement in cytogenetic findings, a decision was made to continue with two consolidations with daunorubicin (150 mg/m²) plus ATRA. Subsequently, she was started on maintenance chemotherapy with 6-MP, Methotrexate, and ATRA. A subsequent bone marrow aspirate on day 125 showed cytogenetic evolution (see below for details of cytogenetics) and morphological relapse (82 % of total leukocytes were myeloblasts/promyelocytes). She was readmitted to the hospital with morphological relapse for reinduction with FLAG (Fludarabine 30 mg/m² days 1–5, Cytarabine 2 g/m² days 1–5, and Filgrastim until neutrophil recovery) without achieving remission. She was then started on arsenic trioxide (0.15 mg/kg/day) on day 157 but developed a complete heart block and acute renal failure 6 days later, and a decision was made to withdraw care. She died 180 days after diagnosis.

Molecular cytogenetics results

Diagnosis

Interphase FISH analysis of 200 cells was performed on the bone marrow aspirate using *PML-RARA* dual color and dual fusion translocation probes (Abbott Molecular, Abbott Park, Illinois), which demonstrated no abnormality. The lack of *RARA* rearrangement (break apart or fusion) was confirmed by FISH using the *RARA* break apart and dual color probe (Abbott Molecular).

G-banding analysis showed a complex karyotype characterized by the absence of the classic *t(15;17)* but with *der(5)t(5;17)(q13;q21)*, monosomy 17, deletion 9q22, and 14–100 dmin (Table 1 and Fig. 2a, f).

Table 1 Cytogenetic, morphological and clinicopathological findings in our case

	Karyotype % (abnormal/total cells)	FISH amplification of MYC		Morphological & clinical correlates
		Whole probe (red/green); % ^a (range) ^b	3' of the probe (red); % ^a (range) ^b	
At diagnosis				
Day 1	45,XX,der(5)t(5;17)(q13;q21),-17, ~14-100 dmin[cp15]/45,XX,idem, ~50-100 dmin[cp2] (100 %; 25/25)	41 (30–50)	59 (30–50)	80 % myeloblasts/promyelocytes induction with daunorubicin + cytarabine. ATRA added on Day 20
Repeat assessments				
Day 30 Unstimulated blood	46,XX,der(5) ^c , -17,+mar, ~8-50dmin[cp5]/46,idem, del(9)(q22)[1]/46,XX[19] (24 %; 6/25)	3.5 (9–11)	8 (30–50)	<5 % myeloblasts/ promyelocytes. 1st consolidation (daunorubicin + ATRA)
Day 90 Bone marrow	44 ~ 46,XX,der(5) ^c ,del(9)(q22) del(13)(q22),-14,-17,+mar, 6 ~ 89 dmin[cp12]/46,XX[13] (48 %; 12/25)	0.5 ^d (~50)	14.5 (10–50)	<3 % myeloblasts promyelocytes 2nd consolidation (daunorrubicin + ATRA)
Day 125 Bone marrow	44-46,XX,-X,der(5) ^c ,del(9)(q22) add(11)(q23),+del(13)(q14q22),-14, dup(15)(q11.2q15),-17, add(17)(p11.2),add(19)(q13.4),+mar, ~2->100dmin[cp25] (100 %; 25/25)	3 (~20)	84.5 (10-100)	>80–90 % myeloblasts/ promyelocytes. 1st reinduction with fludrabine, cytarabine & filgrastim
Day 157 Bone marrow	41-46,XX,del(1)(q32),der(5) ^c , -7, -del(9)(q22),add(11)(q23),-14,-17, add(17)(p11.2),add(19)(q13.4), +21, +mar1,+mar2,7-56dmin[cp8] (100 %; 8/8)	3.5 (10–100)	81 (10–100)	70–80 % myeloblasts/ promyelocytes. 2nd reinduction with Arsenic trioxide. died on day 180

^a Percent of 200 cells with amplified signals^b Range of number of FISH signals^c der(5): der(5)t(5;17)(q13;q21)^d 1 of 200 cells had ~50 red/green signals

To further delineate the der(5), metaphase FISH was done using a Miller-Dieker/Lissencephaly (*LIS1*) region probe set with a SpectrumOrange probe for the *LIS1* (17p13.3) and SpectrumGreen probe for *RARA* (17q21) (Abbott Molecular). It should be pointed out that while the short arm of the der(5) was slightly larger than that of chromosome 17, the two chromosomes could not be readily distinguished from each other due to similar overall length and G-banding pattern, especially in the cells with short chromosomes and suboptimal banding quality (Fig. 2f). The *LIS1* (17p13.3) was used to help differentiate der(5) from chromosome 17. Figure 2f (middle) showed intact orange *LIS1* and green *RARA* signals on chromosome 17 but only the green *RARA* in der(5). This confirmed translocation of the 17q segment containing *RARA* to the der(5) with the breakpoint being proximal to *RARA*. Furthermore, FISH using *RARA* break apart and dual color probes showed normal pattern in interphase cells and the presence of an intact *RARA* signal in both der(5) and chromosome 17 in metaphase cells and no evidence of *RARA* break apart or fusion (Fig. 2f;

lower). The metaphase FISH results explain the presence of two intact *RARA* signals in all interphase cells despite monosomy 17 detected in all G-banded metaphase cells.

To characterize the dmin, FISH was performed using a *MYC* (8q24) break apart and dual color probe set (Cytocell; LPH010; Rainbow Scientific Inc., Windsor). The Cytocell product consists of two probes spaced 712,133 bp apart. The proximal red probe (173 Kb; chr 8: 128248316-128421245) is located 332 Kb 3' of the *MYC* gene, while the distal green probe (186 Kb; chr8: 129133378-129319742) is 380 Kb 5' of the gene. The FISH showed that 41 % of the 200 cells had 30–50 red/green fusion signals, indicative of amplification of the whole probe, while 59 % of the cells had 30–50 red signals, indicative of amplification of 3' of the probe (Fig. 2d). Notably, all interphase and metaphase cells with amplification of red 3' of the probe had only one red/green fusion signal (arrow in Fig. 2b–d), indicative of a deletion of the *MYC*. The *MYC* deletion was confirmed by FISH using a 3-color probe set with *MYC*(8q24)/orange, *CEP8*/aqua, and *IGH*(14q32)/green

Fig. 2 **a** G-banded metaphase cell showing ~100 double minutes. **b–d** FISH using MYC break apart and dual color (red/green) probe set and showing **d** amplification of the whole (red/green) probe in one interphase cell (lower) and amplification of red 3' of the probe in another interphase cells (upper, middle) and amplification of red 3' of the probe in an interphase cell (lower), and **b** amplification of red 3' of the probe in a metaphase cell. Only one red/green signal (arrow) was seen in all cells with amplification of red 3' of the probe in **b–d**, indicative of MYC deletion. **e** Metaphase FISH using probes for MYC (red, 8q24), cen8 (aqua, centromere 8), and IGH (green, 14q32) and showing (1)

MYC amplification (red) on dmin, (2) a normal chromosome 8 (red arrow) with intact cen8 (aqua) and MYC (red) signals, and (3) a deleted chromosome 8 (white arrow) with cen8 (aqua) but loss of MYC signal. **f** upper: G-banded chromosomes 5, der(5)t(5;17)(q13;q21) and 17; middle: FISH using LSI LIS1 (17p13.3, SpectrumOrange) and RARA (17q21.1; SpectrumGreen) and showing a normal 17 with both orange and green probes and der(5) with RARA and confirming translocation of RARA to der(5) and the breakpoint being proximal to RARA; lower: FISH using break apart and dual color (red/green) probe and showing an intact probe in both der(5) and chromosome 17 and no evidence of break apart or fusion of RARA

(Abbott Molecular). The metaphase FISH showed absence of MYC signal in one chromosome 8 in all cells with multiple orange dmin or MYC amplification (Fig. 2e).

Evaluation during clinical course

Four cytogenetic and FISH evaluations were performed on day 30, 90, 125, and 157 during the 6-month clinical course. The evaluations showed dynamic changes in (1) types of chromosome aberrations and (2) the proportion of the two cell lines with the amplification (Table 1).

G-banding analysis of unstimulated blood on day 30 showed the same types of abnormalities as seen at diagnosis, but the proportion of abnormal cells decreased to 24 % (6/25) from the previous 100 % (25/25). Of the six abnormal cells, five (20 %) cells had ~8–50 dmin, a decrease from the previous ~14–100 dmin. Similarly, cells with FISH

amplification of red 3' of the probe decreased to 8 % from 59 %, and cells with FISH amplification of the whole probe decreased to 3.5 % from 41 %. Of note, copy number of the amplified whole probe decreased to 9–11 from the previous 30–50.

The last three evaluations showed continuing cytogenetic evolution with additional aberrations emerging with each subsequent test: deletion 13q, monosomy 14, and an extra marker on day 90; loss of X, additions in 11q23, 17p11.2, and 19q13.4, and duplication of 15q11.2q15 on day 125; and deletion 1q, monosomy 7, trisomy 21, and a second marker on day 157. The incidence of abnormal cells by G-banding was 48 % (12/25) on day 90 and then increased to 100 % (25/25) on day 125 and (8/8) on day 157. FISH amplification of the whole MYC probe was seen in 0.5 % of the cells on day 90 and ~3 % on days 125 and 157, while amplification of 3' of the probe was seen in 14.5 % of the

cells on day 90 and then increased to >80 % on days 125 and 157.

Discussion

To the best of our knowledge, the present case is the second reported APL-like case without *PML-RARA* fusion but with a der(5)t(5;17)(q13;21) as part of a complex karyotype and *MYC* amplification and deletion. A previous APL case with der(5)t(5;17)(q13;21), del(8)(q22q24), der(17), 5–32 dmin was RT-PCR negative for *PML-RARA*, *PLZF-RARA*, *NPM-RARA*, *NuMA-RARA*, and *STAT5b-RARA* [10, 15]. The presence of der(5)t(5;17) at diagnosis and/or relapse in the previous cases and that of our results suggests that the der(5) is a primary aberration. More case reports and molecular cytogenetic studies would help address the question of whether or not the der(5) with a reunion of the cytogenetic segments 5q13::17q21 generates a gene fusion product/protein and/or plays a role in tumorigenicity.

MYC amplification has been reported in at least eight AML cases with promyelocytic differentiation, including the present case (Table 2). Four of the six cases tested by FISH had *MYC* deletion [7, 10, 13, and present case], and one case had monosomy 8 by G-banding [9]. Interestingly, trisomy 8, the most common finding in AML, is absent in all of the eight cases. A majority of the eight cases demonstrated amplification as well as deletion of *MYC*. This suggests a significant role of *MYC* deletion in *MYC* amplification in these APL-like cases and supports the hypothesis of a sequence of deletion, replication, looping, and then amplification of the *MYC* region [18]. Our FISH showed that the amplification signals were on dmin and distributed more or less evenly throughout the interphase and metaphase cells in both cell lines (see Fig. 2). This is different from the previous findings by Frater et al. [7] and Bruyere et al. [8] in that dmin were often seen at periphery of the nuclei or assembled together in metaphase cells and appeared to be eliminated or expelled from some cells in the form of a *MYC*-positive micronuclei or ball. The elimination and exclusion of the

Table 2 Reported AML cases with promyelocytic differentiation and double minutes and *MYC* amplification

Reference	Sex/age	Karyotype	FISH <i>PML-RARA</i> fusion	FISH <i>MYC</i> amp/del	Other tests	Outcome
Karyotype et al. 1993 (9)	F/59	42-45,XX,-5,+6,-8,add(9)(p?), del(10)(q24),der(16)t(8;16)(q22;q24) del(18)(p11), der(20)t(17;20)(q21;q11)-22,+mar,10-100dmin			PCR; <i>MYC</i> amp	Died from CNS involvement 6 wk after dx
Brunel et al. 1995 (10)	F/76	45,XX,der(5)t(5;17)(q?;q21), del(8)(q22q24),-17, del(8)(q22q24),-17,	No	Yes/Yes	Southern blot; <i>RARA</i> intron 2 rearrangement	Died day 14 Corynebacteria septicemia
Frater et al. 2006 (7)	M/78	46,XY[20]/46,XY, del(8)(q24.2), ~2-20dmin[10]	No	Yes/Yes		Complete remission at 9 mo
Grimaldi et al. 2007 (11)	F/67	44,X,-X,add(7)(q32),-9, der(12)t(12;17)(p13;q11.2), dup(17)(q21),-17,-21,+mar1,+mar2,+dmin[9]/46,XX		Yes/?		Patient treated with chemotherapy
Kamath et al. 2008 (12)	F/87	43,X,-X,-9,del(9)(?p21), der(15)t(15;17)(p10;q10), -17,2-60dmin[21]		Yes/No		Died wk after dx
Bruyere et al. 2010 (8)	M/61	46,XY,del(9)(p21),4-30dmin	No	Yes/No		Died 8 mo after dx
Zuberi et al. 2010 (13)	F/57	46,XX,del(8)(q24.2),?del(14)(q11.22q11.22),t(15;17)(q22;q21)[4]/46, idem,2 ~ 20dmin[16]	Yes	Yes/Yes		Rapid response to indication
Present case	F/62	45,XX,der(5)t(5;17)(q13;q21),-17, ~14-100 dmin[cp15]/45,XX,idem, del(9)(q22)[cp8]/90,XX,idemx2, ~50-100 dmin[cp2]	No	Yes/Yes		Died of complete heart block 6 mo after dx

FISH, fluorescence in situ hybridization, *F* female, *M* male, *PCR* polymerase chain reaction, *CNS* central nervous system, *amp* amplification, *del* deletion, *wk* week, *dx* diagnosis, *mo* month, ? unknown

^a This case was later reported as case 55/M3r by Grimwade et al. 2000 with der(5) interpreted as der(5)t(5;17)(q13;q21) and RT-PCR negative for *PML-RARA*, *PLZF-RARA*, *NPM1-RARA*, *NuMA-RARA*, *STAT5b-RARA* (15)

MYC-amplified genetic material might occur before or during treatment in the patient [7] or in vitro experiment with HL-60 cell line [17] and might be one of possible mechanisms for cytogenetic response [7].

It is difficult to assess clinical significance of *MYC* amplification in these APL-like cases because of variations in patient history, clinicopathologic presentations, cytogenetic findings, and treatment. Nevertheless, review of the eight APL-like cases with *MYC* amplification showed that two cases had unfavorable results; one patient died of CNS involvement 6 weeks after diagnosis [9] and another died of infection on day 14 [10]. In two other cases, one with t(15;17) and *PML-RARA* fusion [13] and another without [7], had a rapid response to induction. These findings suggest that *MYC* amplification alone may not be a reliable prognostic indicator in the APL-like cases although it has been linked to poor prognosis in some cases of MDS and AML (most commonly M2) [16, 18]. Notably, the classic t(15;17) and/or *PML-RARA* fusion, a diagnostic hallmark in APL, is absent in seven (78.5 %) of the eight APL-like cases with *MYC* amplification (see Table 2). There appears to be some degree of “mutual exclusion” between *MYC* amplification and t(15;17) and/or *PML-RARA* fusion in these cases. Since *PML-RARA* fusion is the target for ATRA treatment, lack of the *PML-RARA* in these patients may be one of the reasons why most patients demonstrated a lack of response with conventional treatment.

It is well known that complex cytogenetic abnormalities are also associated with adverse prognosis in patients with acute leukemia. Six of the eight cases with *MYC* amplification had a complex karyotype (Table 2). The eight cases implicated a total of 22 chromosome aberrations as identified by G-banding. Deletion 17p and/or monosomy 17 were seen in four cases; deletion 9p and/or monosomy 9 in three cases; and der(5)t(5;17)(q13;q21) in two cases. Notably, three patients with the chromosome 9 aberrations died between 6 weeks and 8 months after diagnosis [8, 9, 12]. Two patients without the chromosome 9 aberrations and deletion 17p/monosomy 7 had a rapid response to induction. These findings suggest that deletion 9p/monosomy 9 and deletion 17p/monosomy 17 are often associated with APL-like cases having *MYC* amplification [8] and poor prognosis.

In conclusion, acute leukemia cases with similar morphology to APL and non-diagnostic chromosomal rearrangements (e.g., der(5)t(5;17), deletions of chromosomes 9 and 17, and dmin) and lacking the classic t(15;17) do occur. It is unclear if an APL-treatment strategy (e.g., therapy including ATRA or AsO3) should be implemented for those cases, but prognosis appears to be poor irrespective of therapies used.

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