Leukemia Research Reports 9 (2018) 65–71

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Secondary clonal hematologic neoplasia following successful therapy for acute promyelocytic leukemia (APL): A report of two cases and review of the literature

Daria Gaut[a], Joshua Sasine[b], Gary Schiller[b,*]

[a] Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, LA, California, USA
[b] Division of Hematology/Oncology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, LA, California, USA

ARTICLE INFO

Keywords:
Acute myelocytic leukemia (AML)
Secondary clone
Myelodysplastic syndrome (MDS)
Therapy-related acute myelocytic leukemia (t-AML)
Therapy-related myelodysplastic syndrome (t-MDS)

ABSTRACT

Although rare, secondary clonal hematologic neoplasia may occur after successful therapy for acute promyelocytic leukemia (APL). These secondary clonal events may be considered therapy-related, but may also be due to an underlying background of clonal hematopoiesis from which both malignancies may develop. In this manuscript, we describe two patients with secondary clones after APL therapy characterized in one patient by deletion of chromosome 11q23 and, in the other, by monosomy of chromosome 7, and also provide a review of all secondary clonal disorders described after APL therapy. We suggest that since most reports identify karyotypic abnormalities not typically associated with chemotherapy, there may be another mechanism underlying secondary clonal development after complete response to initial APL therapy.

1. Introduction

Acute promyelocytic leukemia (APL) is a biologic and clinically well-defined subtype of acute myeloid leukemia typically characterized by the balanced translocation of chromosomes 15 and 17 resulting in fusion of the promyelocytic (PML) and retinoic acid receptor alpha (RARalpha) genes. The disease is also characterized by an unique response to the differentiating agent all-trans retinoic acid (ATRA). Combination therapy of ATRA with either chemotherapy or arsenic trioxide (ATO) has made APL a highly curable leukemia [1–3]. Nevertheless, relapses occurring after a complete remission (CR) of APL do occur and usually derive from their original APL [4]. Secondary myelodysplastic syndrome (MDS) or acute myelocytic leukemia (AML) developing in APL patients in complete remission (CR) is rare but has been documented. Here we describe two patients who initially were diagnosed with acute promyelocytic leukemia (APL) and later relapsed with a distinct neoplastic hematopoietic clone that was not, on simple cytogenetic findings, ancestrally related to the original APL.

2. Case reports

The first patient was a 76-year-old woman with a past medical history of hypertension, diabetes, hypothyroidism, berylliosis requiring corticosteroids, and renal insufficiency who originally presented in February of 2009 with dizziness and orthostatic hypotension. Laboratory studies revealed pancytopenia with blasts on the peripheral blood smear. Bone marrow biopsy showed acute promyelocytic leukemia and t(15:17) was detected with fluorescence in situ hybridization (FISH). Her disease was characterized as intermediate-risk with a white blood cell count of 1.5×10^3/uL and a platelet count of 34×10^3/uL [5]. She received induction chemotherapy with all-trans retinoic acid (ATRA) 45 mg/m^2/day and idarubicin 12 mg/m2 × 4 doses, achieving complete remission, followed by consolidation chemotherapy consisting of intermittent ATRA and idarubicin 5 mg/m2 × 4 doses. Following recovery of blood counts, idarubicin was discontinued due to cardiomyopathy (ejection fraction 39%) and consolidation continued with arensic trioxide (ATO) 45 mg daily for 5 days per week for an abbreviated course of 3 weeks. Maintenance therapy with methotrexate 15 mg weekly and ATRA 50 mg twice daily continued for 18 months. Two years following completion of maintenance therapy, she developed thrombocytopenia with bone marrow biopsy negative for recurrent leukemia. Seven years following her initial remission, she developed anemia as well. Bone marrow biopsy at this time revealed 20–25% myeloid blasts and cytogenetic testing identified deletion of

Abbreviations: AML, acute myelocytic leukemia; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; ATG, antithymyocyte globulin; CR, complete remission; FISH, fluorescence in situ hybridization; 6-MP, 6-mercaptopurine; MDS, myelodysplastic syndrome; PML-RARalpha, promyelocytic leukemia/Retinoic acid receptor alpha; t-AML, therapy-related acute myelocytic leukemia; t- MDS, therapy-related myelodysplastic syndrome

* Corresponding author.
E-mail addresses: dgaut@mednet.ucla.edu (D. Gaut), jsasine@mednet.ucla.edu (J. Sasine), gschiller@mednet.ucla.edu (G. Schiller).

https://doi.org/10.1016/j.lrr.2018.04.005
Received 16 January 2018; Received in revised form 16 March 2018; Accepted 7 April 2018
Available online 16 April 2018

chromosome 11q23 in 7 out of 20 metaphase cells examined, but FISH was negative for the t(15;17) translocation. Next-generation DNA sequencing was performed on the Illumina Miseq to identify somatic variants in 54 of the most commonly mutated genes in myeloid malignancies, and mutations in Additional Sex combs-like Transcriptional Regulator 1 (ASXL1), PHD finger protein 6 (PHF6), and TET methylcytosine dioxygenase 2 (TET2) were also detected. Reinduction with cytarabine 200 mg/m^2 × 7 days and idarubicin 12 mg/m^2 × 3 days was attempted without remission. Karyotype then revealed deletion of the long arm of chromosome 7 (del 7q22) in 19 or 20 metaphase cells analyzed. Decitabine therapy produced a modest response, and she died after further attempts at reinduction.

The second patient was a 65-year-old man who originally presented in December of 2014 with fevers, fatigue, thrombocytopenia, anemia, and leukocytosis. Peripheral blood smear revealed blasts with Auer rods, and bone marrow biopsy demonstrated acute promyelocytic leukemia with t(15;17) present. His disease was characterized as high-risk given a white blood cell count of 56.1 × 10^3/uL [5]. The patient initially received ATRA 45 mg/m^2/day and ATO 0.15 mg/kg daily but developed symptomatic QT prolongation and proceeded to treatment with idarubicin. His course was complicated by prolonged neutropenia with Pseudomonas bacteremia and Aspergillus pneumonia requiring filgrastim and granulocyte transfusions. Bone marrow biopsy following induction was negative for blast cells with normal molecular pathology and negative FISH testing for the t(15;17) translocation. He received three cycles of consolidation consisting of ATRA with idarubicin, mitoxantrone, and cytarabine followed by maintenance therapy with methotrexate 15 mg weekly, 6-mercaptopurine (6-MP) 50 mg daily, and intermittent ATRA 50 mg bid. One year into maintenance, the patient developed pancytopenia, and methotrexate and 6-MP were stopped. A short time later, he developed intermittent right facial paresthesia. MRI brain was concerning for hypointensity over the cerebellum, reflective of subarachnoid bleeding, and hyperintensity in some regions. Lumbar puncture revealed 78% promyelocytes with cytogenetics from cerebrospinal fluid positive for t(15;17). Bone marrow biopsy showed no evidence of blasts, but the karyotype disclosed a new set of anomalies with monosomy of chromosome 7 and an extra marker chromosome in 18 of 20 cells observed (+mar(18)). There were no marrow cells with t(15;17) by FISH or routine karyotype. Hematologic malignancy sequencing panel noted two mutations in the SET binding protein 1 (SETBP1) with allele frequency 36% and 12%. The patient was treated with intrathecal methotrexate 12 mg and intrathecal cytarabine 100 mg followed by whole brain radiation, 2 Gy x 9 fractions. Repeat bone marrow biopsy one month later revealed no excess blasts by flow cytometry, but the karyotype showed persistent monosomy 7 and an extra marker chromosome in all 20 cells observed (+mar(20)). The patient received systemic chemotherapy consisting of cytarabine 100 mg/m^2 × 7 days and daunorubicin 60 mg/m^2 followed by allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning of busulfan, fludarabine, and antithymocyte globulin (ATG). Post-bone marrow transplant bone marrow biopsy showed no evidence of disease and full donor chimerism. Repeat MRI brain/orbits showed resolution of previously seen enhancement. The patient is doing well 10 months post-bone marrow transplant.

3. Discussion

We describe two patients who developed distinct AML clones without t(15;17) following treatment for APL. Such secondary clonal hematologic neoplasia occurring after successful therapy for APL is rare but has been documented, and these cases are illustrated in Table 1 [6–34]. Frequencies ranging from 1–9.8% [18,20,29,33] have been reported with a median latency period of 35.6 months (range 1–158 months) after remission of APL. Two separate hypotheses can describe this observation of the secondary clonal hematologic neoplasia: (1) these diseases may be an outgrowth of an existing undetectable subclone or (2) they may be two independent clones evolved from separate hematopoietic stem cells, likely a result of toxicity from chemotherapy.

The well-described entities of therapy-related myelodysplasia (t-MDS) and acute myeloid leukemia (t-AML) are known to occur following therapy with either alkylating agents or topoisomerase II inhibitors [35,36]. They are characterized by distinct cytogenetic abnormalities: loss of chromosome 5 or 7 with alkylating agents [37,38] and 11q23 and 21q22 aberrations with topoisomerase II inhibitors [39,40]. The most common primary therapies for APL include anthracyclines, which are believed to work through topoisomerase II enzyme inhibition, in addition to 6-MP, methotrexate, and ATRA. It has been hypothesized that methotrexate, 6-MP, or ATRA might modify anthracycline leukemogenesis and contribute to the development of a secondary leukemia [7,10,16,21]. Alkylating agents, however, are not commonly used therapies for APL. Indeed, out of the cases reported of secondary clones following APL therapy, only 4 received an alkylating agent (cyclophosphamide). However, the karyotypes of the secondary clones, including those not treated with alkylating agents, most commonly had characteristics typically associated with prior therapy with an alkylating agent: 16 patients had deletion of all or part of chromosome 7 [6,10,11,13,14,16–19,21,26,29,31] and 15 patients had deletion of all or part of chromosome 5 [6,7,16–18,20,21,29,33]. Despite the fact that all patients were treated with topoisomerase II inhibitors (anthracyclines), only 4 patients, or 6 including our patients, presented with karyotypes typical of prior therapy with a topoisomerase II inhibitor [17,28,29]. Almost half of the patients (23) did not have karyotypic abnormalities at all associated with t-MDS/t-AML. This result suggests either that anthracycline therapy may induce such alkylating agent-type karotypic aberrations in APL patients [32] or that the secondary clones were not in fact therapy-induced. Another possibility to consider is induction of a selective advantage to pre-existing hematopoietic stem cell subclones carrying certain mutations, such as *TP53* or *SETD2*, that allowed them to expand preferentially after treatment [41,42].

Such secondary clones detected after APL therapy may have been derived from an ancestral pre-leukemia stem cell that developed into APL and thereafter contributed to the second disorder. Clonal evolution has been well-defined in AML [43,44] and has also been described in APL [45,46]. A similar theory has been proposed for secondary unrelated clones in CML patients that developed deletions of chromosome 5 and 7 after CML treatment with interferon alpha or imatinib mesylate in the absence of chemotherapy [47,48]. The fact that many patients presented with secondary myelodysplasia may yield support for this theory of clonal evolution. Of the 50 cases of secondary clonal neoplasia following APL treatment reported in the literature, more than half (28) developed myelodysplasia. Furthermore, selected cases of initial diagnosis of APL with concurrent myelodysplastic changes have been reported [8], though it is uncommon.

Going against the theory of clonal evolution and more in support of chemotherapy-induced secondary MDS/AML is the fact that no cases of secondary AML have been reported after arsenic/ATRA therapy for APL without exposure to chemotherapy. However, given that this therapeutic regimen has only recently become standard practice [49], there may not yet have been sufficient time to observe such secondary malignancies. Indeed, the majority of the patients in Table 1 were treated prior to this new therapy.

4. Conclusion

In conclusion, secondary clonal hematologic neoplasia following APL treatment is increasingly being reported. We have described an additional two patients with such a phenomenon. Further research is needed to determine the causality of such secondary clones in terms of relation to chemotherapy versus a common leukemic progenitor and to assess its clinical implications.

Table 1
Literature review of secondary MDS/AML following treatment for APL.

Reference	Initial karyotype	Year of Diagnosis	APL risk stratification	Therapy for APL				Time of relapse after CR (months)	Relapse Disease: MDS or AML	Relapse karyotype	Survival after emergence of second clone
				ATRA	Topoisomerase II Inhibitors	Alkylating Agents	Allogeneic SCT				
6	46XY, t(15;17)(q21;q11)[19] /46,XY,inv(6)(p24q13), t(15;17)(q21;q11)[39]	Unknown	Intermediate	X	X (idarubicin, mitoxantrone)			4	MDS→AML	44,X,-Y,−7 [41]	Expired 1 year later
6	t(15;17)(q22;q11) in 94% of studied cells	Unknown	Intermediate	X	X (idarubicin, mitoxantrone)			20	MDS	46,XX,del(5)(q13q33)	Alive, unknown amount of time later
7	46,XX,t(15;17)(q22;q21)	1997	Intermediate or low	X	X (idarubicin, etoposide)			26	MDS→AML (M6)	46,XX,−5,add(6)(p23-25), + 8,add(17)(p13) [10]	Expired 7 months later
8	46,XY,t(15;17)(q22;11) [20]	1987	Low		X (daunorubicin, etoposide)			33	MDS→AML (M1)	46 XY,t(7;21)(q31;q22) [13]	Expired 75 months later
9	46,XY,t(15;17)	1987	Low		X (daunorubicin, aclarubicin, mitoxantrone, etoposide)			43	AML	46,XY,t(3;21)(q26;q22), der(4)t(4;?)(q27;?),der(7) t(4;7)(q27;q22), der(16)t(16;?)(p11.2;?) [20]	Expired 5 months later
10	46,XY,t(15;17)	1992	Low	X	X (idarubicin)			32	MDS	46,XX,−7, + marker[10]/ 45,XX,−7[7]/ 46,XX[3]	Alive 1 year later
11	46,XY,t(15;17)(q22;q12)	Unknown	Unknown		X (idarubicin, doxorubicin, etoposide)	X (cyclophosphamide)		26	Biphenotypic leukemia	45,XY,−7[7]	Palliative care 15 months later
12	46,XX,t(15;17)(q22;q21)	1984–1991	Intermediate or low		X (idarubicin, etoposide)		X	49	AML (M4)	46,XX,t(10;11)(p14;q21)	Expired 2 months later
13	46,XY,t(15;17)	Unknown	Unknown		X (idarubicin, mitoxantrone)		X	36	AML	45,XY,−7	Expired at unclear date
14	46,XX,t(15;17)(q22;q21)	Unknown	Intermediate or low		X (daunorubicin)	X (cyclophosphamide)		24	MDS (RAEB)→AML (M2)	45,XX,dic(5;17)(q11;p11)/ 43, idem,−7,−20	Expired 6 months later
15	46,XY,t(15;17)(q22;q21)	Unknown	Unknown		X (etoposide)	X (cyclophosphamide)		43	AML (M2)	46,XY,t(10;11)(q23;p15)	Alive 26 months later
16	47,XX, + 8,t(15;17)(q22;q21)	1993	High	X	X (daunorubicin)			29	MDS (RAEB)	45,XX,−5,−7, + 11 [6]/ 47,XX, + 8,t(15;17)(q22;q21) [14]	Expired 5 months later
16	46,XX,−3(q24;q26), −5(q23;q32), t(7;11)(p11; p12), t(15;17)(q22;q21)	1996	High	X	X (daunorubicin)			23	MDS (RAEB)→ M0 AML after 6 months	45, XX,−7	Expired 11.5 months later
17	46,XX,t(15;17)	1992	High		X (daunorubicin, mitoxantrone, etoposide)			~84	MDS RAEB	43–45XX, del(5)(q15)[8],−7[7], + 9(q34)[3],−18[4],−21[5], + mar[3], + r[2], + dmin[3][cp8]	Expired 3 months later
18	46,XX,t(15;17)	1989–1993	Low		X (idarubicin)			48	MDS detected concomitantly with AML (M4)	46,XX,t(10;11)(p14;q21)	Expired of GVHD (day + 50)
18	46,XX,t(15;17)	1989–1993	Low	X	X (idarubicin)			43	MDS→AML	45,XX,−7	Alive 18 months later
18	46,XY,t(15;17)	1989–1993	Low	X	X (idarubicin)			46	MDS	N/A (lack of evaluable metaphase)	Expired 1 month later
18	46,XY,t(15;17)	1989–1993	High		X (idarubicin)			48 (33 from second CR)	MDS→AML	46,XY,del(5q-)	Expired 5 months later
18	46,XX,t(15;17)	1989–1993	High	X	X (idarubicin)		X	24 (2 from second CR)	MDS	46,XX	Alive 12 months later

(*continued on next page*)

Table 1 (*continued*)

Reference	Initial karyotype	Year of Diagnosis	APL risk stratification	Therapy for APL				Time of relapse after CR (months)	Relapse Disease: MDS or AML	Relapse karyotype	Survival after emergence of second clone
				ATRA	Topoisomerase II Inhibitors	Alkylating Agents	Allogeneic SCT				
19	46,XX,t(15;17) Expired 9 months later	2000	Intermediate	X	X (idarubicin, etoposide)			52	MDS	46,XX,del(2q-),del7(q31)	
20	46,XX,t(15;17)(q22;q21)	1991–1998	Intermediate or Low	X	X (daunorubicin)			13 after original APL diagnosis, additional APL relapse 7 months after MDS diagnosis	MDS (RA)	46, XX, del(5)(q22q34),(t15;21)(p11; q21), − 17, + mar	Expired 25.4 months later
20	46,XY,t(15;17)(q22;q21)	1991–1998	Intermediate or Low	X	X (daunorubicin, mitoxantrone and idarubicin at relapse)	X (cyclophosphamide at relapse)	X (for relapse)	46 (6 from second CR)	MDS (RAEB)→ M0 AML after 1 month	43,XY,del(5)(q12q35),add(11)(q23), dup(12)(q12q22), − 17, − 18, − 22	Expired 0.8 months later
20	46,XY,del(9)(q21q31), t(15;17)(q22;q21)	1991–1998	Intermediate or Low	X	X (daunorubicin)			111	MDS (RA)	45,XY, − 5,der(7)t(7;20) (q11;p? or q?), der(10)t(7;10;20)(q3?;q2?;p? or q?), − 13,der(17)t(10;17) (q2?;p11), − 20, del(20)(q11), + mar1, + mar3/ 47, idem,del(X)(q26), der(1) (1;?)(p36;?), + 8, + mar2	Alive 24 months later
20	Failure	1991–1998	Intermediate or Low	X	X (daunorubicin)			74	MDS(RA)→ M0 AML after 18 months	45,XY, − 8,t(8;11)(q32;q21)	Expired 7.5 months later
20	46,XY,t(15; 17)(q22;q21)	1991–1998	Intermediate or Low	X	X (daunorubicin)			47	MDS (RAEB-t)	45,XY,t(3;17)(p11;q11), del(5)(q13q33), del(6)(p22), − 17	Alive 4 months later
21	46,XX,t(15;17)	1996	Intermediate	X	X (idarubicin, daunorubicin)			40	MDS (RAEB)→ M2 AML after 6 months	45,XX,del(4)(q31), − 5, add(5)(q35), − 7,der(17), t(17;?)(p11;?), − 18, + mar1, + mar2[*cp*21]/ 46,XX [4]	Expired 9 months later
22	46,XX,t(15;17)	1999	Unknown	X	X (idarubicin)			18	M4 AML	46,XX,t(9;11)(p12;q23) [24]	Expired a few days after diagnosis
23	46,XY (PML/RARA +)	1995	Intermediate or low	X	X (mitoxantrone, etoposide, daunorubicin)			20	MDS (RAEB)→AML (M2) after 10 months	47,XY, + 8[2]/ 46,XY [18]	Alive, unknown amount time
24	46,XX,i(17)(q10)[20] (PML - RARA +)	2001	Low	X	X (idarubicin)			10	M5 AML	46,XX, t(8;16)(p11.2;p13.3),inv(11) (p15q22 ~ q23)[11]/ 47,idem, + i(8)(q10)[9]	Alive 1 year later
25	46, XY, t(15;17)(q22;q21)	1991	High	X	X (daunorubicin)			6	M3 AML (rare Auer rods)	46,XY,t(3;6)(q26;q15)	Alive 15 months later
26	46,XY,t(15;17)	Unknown	Low	X	X (daunorubicin)			~ 36	M2 AML	45,XY, − 7,t(3;21)(q26;q22)	Expired 2 years later
27	46,XX,t(15;17)	1994	High	X	X (idarubicin, etoposide)			~ 1	NA	46,XX,t(11;19)(q13;q13.3) in 12% of cells	Alive 18 months s/p autotransplantation
28	46,XY,t(15;17)(q22;q21) [24]	1996	Unknown	X	X (idarubicin)			~ 8	NA	46,XY,del(11)(q21)[2]/ 46,XY [50]	Expired at unknown date
28	46,XY,t(15;17)(q22;q21) [18]/ 46,XY[1]	1997	Unknown	X	X (idarubicin, mitoxantrone, etoposide)			~ 1	NA	46,XY,del(11)(q14q23) [1], 46,XY [39]	Alive, 1126 days later
29	46,XY,t(15;17)	1997–2009	High	X				46	NA	46,XY,del(20)(q11)[4]/ 46,XY [38]	Alive 89 days later

(*continued on next page*)

Table 1 (*continued*)

Reference	Initial karyotype	Year of Diagnosis	APL risk stratification	Therapy for APL				Time of relapse after CR (months)	Relapse Disease: MDS or AML	Relapse karyotype	Survival after emergence of second clone
				ATRA	Topoisomerase II Inhibitors	Alkylating Agents	Allogeneic SCT				
29	46,XX,t(15;17)	1997–2009	Intermediate	X	X (idarubicin)			23	NA	46,XX,del(20)(q11)[2]/ 46,XX [36]	Alive 44 days later
29	46,XY,t(15;17)	1997–2009	Unknown	X	X (amsacrine)			8	NA	46,XY,del(11)(q21)[2]/ 46,XY [50]	Expired 10 months later
29	46,XY,t(15;17)	1997–2009	Intermediate	X	X (idarubicin, mitoxantrone)			1	NA	46,XY,del(11)(q14q23)[1]/ 46,XY[39]	Alive 36 months later
29	46,XY,t(15;17)	1997–2009	Intermediate	X	X (idarubicin)			38	NA	47,XY, + 15[2]/ 46,XY[38]	Alive 18 months later
29	46,XY,t(15;17)	1997–2009	Low	X	X (idarubicin)			53	NA	46,XY,t(3;12)(q11.2;q13)[3]/ 46,XY[40]	Alive 20 months later
29	46,XX,t(15;17)	1997–2009	Low	X	X (idarubicin)			23	NA	46,XX,dup(1)(q21q32)[4]/ 46,XX[51]	Alive 24 months later
29	46,XY,t(15;17)	1997–2009	Intermediate	X	X (idarubicin)			22	AML	46,XY,del(5)(q?22),add(7)(q?32)[3]/ 46,XY[35]	Expired 23 months later
29	46,XY,t(15;17)	1997–2009	Intermediate	X	X (idarubicin)			22	MDS	46,XY,del(5)(q13q31)[4]/ 46,XY [46]	Alive 38 months later
29	46,XX,t(15;17)	1997–2009	High	X	X (idarubicin)			30	NA	46,XX,del(7)(q22q36)[3]/, 46,XX[68]	Alive 22 months later
29	46,XX,t(15;17)	1997–2009	Low	X	X (idarubicin)			47	MDS	45,XX, −7[9]/ 45, idem,?idic(X)(q11)[6]/ 46,XX[26]	Alive 37 months later
29	46,XY,t(15;17)	1997–2009	Intermediate	X	X (idarubicin)			30	MDS→AML	45,XY, −5,add(17)(p12)[4]/ 44,sl, −7[2]/45,sdl1, + mar1[2]/ 46,XY[36]	Expired 22 months later
30	46,XX,t(15;17)	Unknown	Intermediate or low	X	X (daunorubicin)			36	AML M2	Normal	Expired within 1 year
31	46,XX,t(15;17)(q22;q21)[10]/ 46,XX [14]	Unknown	Intermediate	X	X (idarubicin, mitoxantrone)			20	MDS	46,X,del(X)(q22q28),t(2;11)(q37;q23),del(7) (q22q36)[9]	Expired 10 months later
32	46,XX,t(15;17)	1988	Intermediate or low		X (daunorubicin)			158	MDS	47,XY, + 1,i(1)(q10)	Alive 37 months later
33	46,XX,t(15;17)	1994	Unknown	X	X (idarubicin)			~24	MDS	45,XX, −5,add(17)(p11.2)	Expired within 1 year
34	46,XY,t(15;17)(q22;q21)	2001	Unknown	X	X (idarubicin)			~36	NA	46,XY,del(20)(q11q13)	Alive, unknown time later

5. Clinical practice points

- Secondary clonal hematologic neoplasia occurring after successful therapy for APL is rare but has been documented.
- We describe an additional two patients with secondary clones after APL therapy characterized in one patient by deletion of chromosome 11q23 and, in the other, by monosomy of chromosome 7.
- A thorough review of the literature suggests that most of these secondary neoplasms contain karyotypic abnormalities not typically associated with chemotherapy, arguing against a therapy-induced mechanism.
- It is possible that such secondary clones instead represent clonal evolution from an ancestral preleukemic stem cell capable of differentiating into both APL and MDS/AML.

Conflict of interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Acknowledgment

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2018.04.005.

References

[1] F. Mandelli, D. Diverio, G. Avvisati, et al., Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano–Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups, Blood 90 (3) (1997) 1014–1021.
[2] M.A. Sanz, G. Martín, C. Rayón, et al., A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group, Blood 94 (9) (1999) 3015–3021.
[3] F. Lo Coco, G. Avvisati, M. Vignetti, et al., Retinoic acid and arsenic trioxide for acute promyelocytic leukemia, N. Engl. J. Med. 369 (2) (2013) 111–121.
[4] G. Avvisati, F. Lo Coco, F. Mandelli, Acute promyelocytic leukemia: Clinical and morphologic features and prognostic factors, Semin. Hematol. 38 (1) (2001) 4–12.
[5] M.A. Sanz, F. Lo Coco, G. Martín, et al., Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups, Blood 96 (4) (2000) 1247–1253.
[6] C. Panizo, A. Patiño, R. Lecumberri, et al., Secondary myelodysplastic syndrome after treatment for promyelocytic leukemia: clinical and genetic features of two cases, Cancer Genet. Cytogenet. 143 (2) (2003) 178–181.
[7] A. Pecci, R. Invernizzi, A therapy-related myelodysplastic syndrome with unusual features in a patient treated for acute promyelocytic leukemia, Haematologica 86 (1) (2001) 102–103.
[8] T. Jubashi, K. Nagai, Y. Miyazaki, et al., A unique case of t(15;17) acute promyelocytic leukaemia (M3) developing into acute myeloblastic leukaemia (M1) with t(7;21) at relapse, Br. J. Haematol. 83 (4) (1993) 665–668.
[9] H. Miyazaki, T. Ino, R. Sobue, et al., Translocation (3;21)(q26;q22) in treatment-related acute leukemia secondary to acute promyelocytic leukemia, Cancer Genet. Cytogenet. 74 (2) (1994) 84–86.
[10] A.W. Bseiso, H. Kantarjian, E. Estey, Myelodysplastic syndrome following successful therapy of acute promyelocytic leukemia, Leukemia 11 (1) (1997) 168–169.
[11] M.S. Felice, J. Rossi, M. Gallego, et al., Acute trilineage leukemia with monosomy of chromosome 7 following an acute promyelocytic leukemia, Leuk. Lymphoma. 34 (3-4) (1999) 409–413.
[12] E. Todisco, A.M. Testi, G. Avvisati, et al., Therapy-related acute myelomonocytic leukemia following successful treatment for acute promyelocytic leukemia, Leukemia 9 (9) (1995) 1583–1585.
[13] G. Meloni, D. Diverio, M. Vignetti, et al., Autologous bone marrow transplantation for acute promyelocytic leukemia in second remission: prognostic relevance of pretransplant minimal residual disease assessment by reverse-transcription polymerase chain reaction of the PML/RAR alpha fusion gene, Blood 90 (3) (1997) 1321–1325.
[14] T. Hatzis, G.R. Standen, R.T. Howell, C. Savill, M. Wagstaff, G.L. Scott, Acute promyelocytic leukaemia (M3): relapse with acute myeloblastic leukaemia (M2) and dic(5;17) (q11;p11), Am. J. Hematol. 48 (1) (1995) 40–44.
[15] H. Sawada, H. Morimoto, A. Wake, Y. Yamasaki, Y. Izumi, Therapy-related acute myeloid leukemia with t(10;11)(q23;p15) following successful chemotherapy for acute promyelocytic leukemia with t(15;17)(q22;q21), Int. J. Hematol. 69 (4) (1999) 270–271.
[16] S. Zompi, O. Legrand, D. Bouscary, et al., Therapy-related acute myeloid leukaemia after successful therapy for acute promyelocytic leukaemia with t(15;17): a report of two cases and a review of the literature, Br. J. Haematol. 110 (3) (2000) 610–613.
[17] W.Y. Au, C.C. Lam, E.S. Ma, C. Man, T. Wan, Y.L. Kwong, Therapy-related myelodysplastic syndrome after eradication of acute promyelocytic leukemia: cytogenetic and molecular features, Hum. Pathol. 32 (1) (2001) 126–129.
[18] R. Latagliata, M.C. Petti, S. Fenu, et al., Therapy-related myelodysplastic syndrome–acute myelogenous leukemia in patients treated for acute promyelocytic leukemia: an emerging problem, Blood 99 (3) (2002) 822–824.
[19] E. Gündüz, O.M. Akay, B. Durak, Z. Gülbaş, Therapy-related myelodysplastic syndrome following acute promyelocytic leukemia and biphenotypic acute leukemia following stem cell transplantation in the same patient, Turk. J. Haematol. 24 (2) (2007) 85–87.
[20] I. Lobe, F. Rigal-Huguet, A. Vekhoff, et al., Myelodysplastic syndrome after acute promyelocytic leukemia: the European APL group experience, Leukemia 17 (8) (2003) 1600–1604.
[21] A. Athanasiadou, R. Saloum, I. Zorbas, et al., Therapy-related myelodysplastic syndrome with monosomy 5 and 7 following successful therapy for acute promyelocytic leukemia with anthracyclines, Leuk. Lymphoma. 43 (12) (2002) 2409–2411.
[22] M. Annunziata, S. Palmieri, B. Pocali, et al., Therapy-related acute myeloid leukemia with t(9;11)(p12;q23) in a patient treated for acute promyelocytic leukemia, Hematol. J. 4 (4) (2003) 289–291.
[23] N. Stavroyianni, X. Yataganas, D. Abazis, C. Pangalos, J. Meletis, Acute promyelocytic leukemia relapsing into FAB-M2 acute myeloid leukemia with trisomy 8, Cancer Genet. Cytogenet. 117 (1) (2000) 82–83.
[24] G.Y. Lee, S. Christina, S.L. Tien, et al., Acute promyelocytic leukemia with PML-RARA fusion on i(17q) and therapy-related acute myeloid leukemia, Cancer Genet. Cytogenet. 159 (2) (2005) 129–136.
[25] F. Desangles, E. Vilain, M. Arborio, T. De Revel, G. Flandrin, t(15;17) hypergranular acute promyelocytic leukemia (M3) developing into a t(3;6) M3 without t(15;17) at relapse, Leuk. Lymphoma. 19 (1–2) (1995) 185–188.
[26] R.D. Betancourt-García, J. Castro, A.C. Fernández, A. López-Enríquez, J. Fradera, E. Pacheco, Acquired acute myelogenous leukemia after therapy for acute promyelocytic leukemia with t(15;17): a case report and review of the literature, P R Health Sci. J. 28 (2) (2009) 146–150.
[27] P. Temperani, M. Luppi, F. Giacobbi, et al., Occurrence of a novel t(11;19)(q13;q13.3) in complete remission of acute promyelocytic leukemia, Cancer Genet. Cytogenet. 101 (1) (1998) 35–38.
[28] L.J. Campbell, K.C. Rayeroux, K. Arkell, J.V. Catalano, M.F. Cole-Sinclair, Appearance of del(11q) in two patients with acute promyelocytic leukaemia treated with all-trans retinoic acid and combination chemotherapy, Br. J. Haematol. 118 (1) (2002) 243–245.
[29] C. Batzios, L.A. Hayes, S.Z. He, et al., Secondary clonal cytogenetic abnormalities following successful treatment of acute promyelocytic leukemia, Am. J. Hematol. 84 (11) (2009) 715–719.
[30] R.K. Sahoo, L. Kumar, R. Kumar, A. Sharma, Acute promyelocytic leukemia relapsing into acute myeloid leukemia-M2 with normal cytogenetics, Indian J. Med. Paediatr. Oncol. 34 (4) (2013) 327–329.
[31] S. Snijder, C.H.M. Mellink, H. van der Lelie, Translocation (2;11)(q37;q23) in therapy-related myelodysplastic syndrome after treatment for acute promyelocytic leukemia, Cancer Genet. Cytogenet. 180 (2) (2008) 149–152.
[32] A. Pawarode, E. Finlay, S.N. Sait, M. Barcos, M.R. Baer, Isochromosome 1q in a myelodysplastic syndrome after treatment for acute promyelocytic leukemia, Cancer Genet. Cytogenet. 167 (2) (2006) 155–160.
[33] G. Garcia-Manero, H.M. Kantarjian, S. Kornblau, E. Estey, Therapy-related myelodysplastic syndrome or acute myelogenous leukemia in patients with acute promyelocytic leukemia (APL), Leukemia 16 (9) (2002) 1888.
[34] M. Mallo, M. Salido, B. Espinet, et al., Could ATRA/Idarubicin treatment of acute promyelocytic leukemia induce the appearance of new clonal cytogenetic abnormalities in patients in complete remission, Leuk. Res. 31 (9) (2007) 1315–1317.
[35] D. Rund, D. Ben-Yehuda, Therapy-related leukemia and myelodysplasia: evolving concepts of pathogenesis and treatment, Hematology 9 (3) (2004) 179–187.
[36] L.A. Godley, R.A. Larson, Therapy-related myeloid leukemia, Semin. Oncol. 35 (4) (2008) 418–429.
[37] S.M. Smith, M.M. Le Beau, D. Huo, et al., Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series, Blood 102 (1) (2003) 43–52.
[38] D. Rund, S. Krichevsky, S. Bar-Cohen, et al., Therapy-related leukemia: clinical characteristics and analysis of new molecular risk factors in 96 adult patients, Leukemia 19 (11) (2005) 1919–1928.
[39] M.K. Andersen, D.H. Christiansen, M. Kirchhoff, J. Pedersen-Bjergaard, Duplication

or amplification of chromosome band 11q23, including the unrearranged MLL gene, is a recurrent abnormality in therapy-related MDS and AML, and is closely related to mutation of the TP53 gene and to previous therapy with alkylating agents, Genes Chromosomes Cancer 31 (1) (2001) 33–41.

[40] J. Pedersen-Bjergaard, S. Timshel, M.K. Andersen, A.S. Andersen, P. Philip, Cytogenetically unrelated clones in therapy-related myelodysplasia and acute myeloid leukemia: experience from the Copenhagen series updated to 180 consecutive cases, Genes Chromosomes Cancer 23 (4) (1998) 337–349.

[41] T.N. Wong, G. Ramsingh, A.L. Young, et al., Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia, Nature 518 (7540) (2014) 552–555.

[42] B.G. Mar, S.H. Chu, J.D. Kahn, et al., *SETD2* alterations impair DNA damage recognition and lead to resistance to chemotherapy in leukemia, Blood 130 (24) (2017) 2631–2641.

[43] L. Ding, T.J. Ley, D.E. Larson, et al., Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing, Nature 481 (7382) (2012) 506–510.

[44] M. Jan, T.M. Snyder, M.R. Corces-Zimmerman, et al., Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia, Sci. Transl. Med. 4 (149) (2012) 149ra118.

[45] X. Zhang, Q. Zhang, J. Dahlström, et al., Genomic analysis of the clonal origin and evolution of acute promyelocytic leukemia in a unique patient with a very late (17 years) relapse, Leukemia 28 (8) (2014) 1751–1754.

[46] N.D. Dimov, L.J. Medeiros, F. Ravandi, C.E. Bueso-Ramos, Acute promyelocytic leukemia at time of relapse commonly demonstrates cytogenetic evidence of clonal evolution and variability in blast immunophenotypic features, Am. J. Clin. Pathol. 133 (3) (2010) 484–490.

[47] L. Fayad, H. Kantarjian, S. O'Brien, et al., Emergence of new clonal abnormalities following interferon-alpha induced complete cytogenetic response in patients with chronic myeloid leukemia: report of three cases, Leukemia 11 (5) (1997) 767–771.

[48] M.K. Andersen, J. Pedersen-Bjergaard, L. Kjeldsen, I.H. Dufva, K. Brøndum-Nielsen, Clonal Ph-negative hematopoiesis in CML after therapy with imatinib mesylate is frequently characterized by trisomy 8, Leukemia 16 (7) (2002) 1390–1393.

[49] L. Cicconi, F. Lo-Coco, Current management of newly diagnosed acute promyelocytic leukemia, Ann. Oncol. 27 (8) (2016) 1474–1481.