A therapy-related myelodysplastic syndrome with unusual features in a patient treated for acute promyelocytic leukemia

Myelodysplastic syndromes (MDS) in patients treated for acute promyelocytic leukemia (APL) are rare events; we report a case that shows how stem cell disorders usually related to exposure to alkylating agents can also be observed after treatment with topoisomerase II inhibitors; we also remark that this phenomenon has been especially observed after treatment for APL.

MDS in patients treated for APL are rare events; we report a case that shows some traits that are unusual among therapy-related stem cell disorders. A 51-year old woman presented in May 1997 with fatigue and dyspnea. Her peripheral blood cell count showed pancytopenia with 2% abnormal promyelocytes; coagulation tests showed signs of disseminated intravascular coagulation. Bone marrow revealed 50% hypergranular promyelocytes; cytogenetic analysis showed the classical translocation t(15;17) while molecular biology studies confirmed the presence of PML/RARα gene rearrangement type bcr3. A diagnosis of hypergranular APL was made. The patient was treated according to the Gimema AIDA protocol; she received induction therapy with ATRA 45 mg/m^2/day plus idarubicin 12 mg/m^2/day for 4 days, achieving complete remission after one month. Consolidation therapy consisted of three courses as follows: cytosine arabinoside (Ara-C) plus idarubicin; mitoxantrone plus etoposide; idarubicin plus Ara-C plus 6-thioguanine. In January 1998 the patient started maintenance therapy consisting of courses of methotrexate plus 6-mercaptopurine alternating with courses of ATRA. Therapy was stopped in July 1999 owing to the appearance of progressive pancytopenia. In September 1999 the bone marrow examination revealed hypocellularity with trilineage dysplasia; 4% of nucleated cells were blasts; Perls' staining revealed the presence of 11% ring sideroblasts. No abnormal promyelocytes were seen. Karyotype was 46, XX, -5, add (6) (p23-25), +8, add (17) (p13) in 10/10 metaphases. The molecular biology study showed that the PML-RARα gene rearrangement was absent. A diagnosis of MDS was made. In December 1999 the MDS evolved into M6 acute myeloid leukemia (AML) refractory to polychemotherapy, and the patient died four months later from infectious complications (Table 1).

Table 1. Laboratory findings during disease evolution.

Date	Clinical stage	Bone marrow cytology	Karyotype	PML/RARα
05/97	APL onset	hypercellularity 50% atypical promyelocytes no myelodysplastic changes	46,XX, t(15;17) (q22;q21)	Present
06/97	CR	normal findings	46,XX	Absent
09/99	MDS	hypocellularity trilineage dysplasia no atypical promyelocytes	46,XX -5, add(6) (p23-25) 8, add (17) (p13)	Absent
12/99	AML	40% myeloblasts erythroid hyperplasia trilineage dysplasia	46,XX, -5, add (6) (p23-25), +8, add (17) (p13)	Absent

PML/RARα = fusion transcript PML/RARα identified by polymerase chain reaction. CR = complete remission.

Seven cases of MDS and seven cases of AML in patients with a previous diagnosis of APL have been reported in the literature (Table 2):[1-10] although several mechanisms have been hypothesized – coexistence of MDS/AML and APL with initial superimposition of APL, MDS/AML as a clonal evolution from the original APL – most of the authors agree in considering these cases as therapy-related secondary MDS and AML (t-MDS and t-AML).

The case we report shows features that are unusual among therapy-related stem cell disorders. The patient developed a hematologic disease usually associated with previous treatment

Table 2. Review of the literature: relationship between therapy for APL and features of secondary disease.

	First diagnosis		Therapy for APL			Latency*	Second diagnosis	
	Disease	Karyotype	ATRA	Anthracyclines and/or etoposide	Alkylating agents	(months)	Disease (FAB)	Karyotype
Jubashi *et al.* (1993)[1]	APL	t(15;17)	-	+	-	37	AML (M1)	t(7;21) (q31;q22)
Myazaki *et al.* (1994)[2]	APL	NA	-	+	-	43	AML (NA)	t(3;21) (q26;q22)
Todisco *et al.* (1995)[3]	APL	t(15;17)	-	+	-	49	AML (M4)	t(10;11) (p14;q21)
Hatzis *et al.*(1995)[4]	APL	t(15;17)	-	+	+	23	AML (M2)	dic(5;17) (q11;p11)
Bseiso *et al.* (1997)[5]	APL	t(15;17)	+	+	-	34	MDS (RAEBt)	-7
Meloni *et al.* (1997)[6]	APL	t(15;17)	-	+	+	36	AML (NA)	-7
Latagliata *et al.* (1999)[7]	APL	t(15;17)	+	+	-	43	MDS (RAEB)	-7
	APL	t(15;17)	+	+	-	46	MDS (RAEB)	NA
	APL	t(15;17)	-	+	+	46	MDS (RAEB)	5q-
	APL	t(15;17)	+	+	+	22	MDS (RA)	normal
Felice *et al.* (1999)[8]	APL	t(15;17)	+	+	+	26	Byphenotypic°	-7
Sawada *et al.* (1999)[9]	APL	t(15;17)	-	+	+	43	AML (M2)	t(10;11) (q23;p15)
Zompi *et al.* (2000)[10]	APL	t(15;17), +8	+	+	-	29	MDS (RAEB)	-5, -7, +11
	APL	t(15;17), 3q-, 5q-, t(7;11)	+	+	-	23	MDS (RAEB)	-7

*NA= not available; *after achieving complete remission.° acute biphenotypic leukemia.*

with alkylating agents – t-AML after a transient period of t-MDS with hypocellular bone marrow and unbalanced complex chromosome aberrations including monosomy 5. However, she was not exposed to alkylating agents and she received anthracyclines and etoposide as major leukemogenic agents. The latent period for the development of t-MDS, 24 months, is compatible with leukemogenesis by these drugs. Analogous observations were made by Zompi *et al.*[10] and Bseiso *et al.*[5]; similar features were presented by one of the cases described by Latagliata *et al.*[7] Thus, even if the occurrence of a t-MDS or t-AML after APL is a rare event, a relatively high frequency of these unusual presentations has been observed. The explanation remains unclear: it was hypothesized that methotrexate and 6-mercaptopurine[10] or ATRA[5] might modify anthracycline leukemogenesis.

In conclusion, stem cell disorders usually related to exposure to alkylating agents can also be observed after treatment with topoisomerase II inhibitors; this phenomenon has been especially observed after treatment for APL.

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References

1. Jubashi T, Nagai K, Miyazaki Y, 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 1993; 83:665-8.
2. Myazaki H, Ino T, Sobue R, et al. Translocation (3;21) (q26;q22) in treatment-related acute leukemia secondary to acute promyelocytic leukemia. Cancer Genet Cytogen 1994; 74:84-6.
3. Todisco E, Testi A, Avvisati G, et al. Therapy-related acute myelomonocytic leukemia following successful treatment for acute promyelocytic leukemia. Leukemia 1995; 9:1583-5.
4. Hatzis T, Standen GR, Howell RT, Savill C, Wagstaff M, Scott GL. Acute promyelocytic leukaemia (M3): relapse with acute myeloblastic leukemia (M2) and dic(5;17) (q11;p11). Am J Hematol 1995; 48:40-4.
5. Bseiso AW, Kantarjian H, Estey E. Myelodysplastic syndrome following successful therapy of acute promyelocytic leukemia. Leukemia 1997; 11:168-9.
6. Meloni G, Diverio D, Vignetti M, 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/RARα fusion gene. Blood 1997; 90:1321-5.
7. Latagliata R, Fenu S, Aloe Spiriti MA, et al. Occurrence of secondary MDS/AML in patients with acute promyelocytic leukemia (APL). Haematologica 1999; 84(Suppl 9):51.
8. Felice M, Rossi J, Gallego M, et al. Acute trilineage leukemia with monosomy of chromosome 7 following an acute promyelocytic leukemia. Leuk Lymphoma 1999; 34:409-13.
9. Sawada H, Morimoto H, Wake A, Yamasaki Y, Izumi Y. Therapy-related acute myeloid leukemia with a t(10;11) (q23;p15) following successful chemotherapy for acute promyelocytic leukemia with t(15;17). Int J Hematol 1999; 69:270-1.
10. Zompi S, Legrand O, Bouscary D, 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 2000; 110:610-3.