Haematologica 1998; 83:471-473 case of the month

T-cell acute lymphoblastic leukemia occurring in a patient with acute promyelocytic leukemia

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ABSTRACT

Secondary acute lymphoblastic leukemia (sALL) following acute myeloid leukemia (AML) is a rare event; only eight cases have been reported. We report a patient with acute promyelocytic leukemia (APL), in hematological and molecular remission who developed T-ALL three years after the diagnosis of APL. The morphological, cytochemical, phenotypical and molecular features of this T-ALL were different from those of the previous APL. The absence of t(15;17), negative PML/RARα at reverse transcription polymerase chain reaction (RT-PCR) analysis and presence of TcRδ support the hypothesis that the T-ALL in this sALL case originated from a different clone from that of the APL cells.

Key words: acute promyelocytic leukemia, secondary acute lymphoblastic leukemia

Acute leukemia has frequently been described to occur after Hodgkin's disease, solid tumors and non-Hodgkin's lymphoma. Most published series have dealt with acute myeloblastic leukemia (AML) whereas secondary acute lymphoblastic leukemia (s-ALL) is rare.[1] Even more so are cases of sALL following AML, both in adults and children. We report herein a patient with classic acute hypergranular promyelocytic leukemia (APL) who developed T-ALL as a second malignant neoplasm three years after the first diagnosis of APL.

Case report

A 25-year-old woman was admitted to our hospital for anemia and leukopenia in September 1992. Hemoglobin level was 7.2 g/dL, leukocyte count 0.4×10^9/L (with 6% polymorphonuclear cells, 89% lymphocytes, 5% promyelocytes) and platelet count 16×10^9/L. The bone marrow (BM) was hypercellular with 87% typical promyelocytes with strong cytochemical positivity to myeloperoxidase (MPO) and chloracetate esterase. Immunophenotyping studies of BM cells revealed that the blasts expressed CD13 (94%) and CD33 (99%) (Table 1). Cytogenetic studies of BM showed a 46, XX, t(15;17) (q22;q21) karyotype in all metaphases analyzed (15/15). Molecular analysis performed by reverse transcription polymerase chain reaction (RT-PCR) revealed the PML/RARα fusion mRNA corresponding to the short (bcr-3) form. The diagnosis of classic APL was made. She achieved complete remission (CR) in November 1992 after induction therapy with idarubicin (IDA) 10 mg/m^2 for 6 days followed by three consolidation courses that included: IDA (32 mg/m^2), mitoxantrone (MTZ) (50 mg/m^2), etoposide (VP-16) (500 mg/m^2), cytosine-arabinoside (ARA-C) (6 g/m^2) and 6-thioguanine (6-TG) (1050 mg/m^2). Therapy was completed in June 1995, at which time the patient demonstrated no evidence of residual disease as assessed by molecular analysis of the PML/RARα fusion mRNA. In September 1995 the patient returned to our hospital for thrombocytopenia (platelet count of 11×10^9/L) and leukocyte count of 9.3×10^9/L with 14% blast cells. BM examination revealed replacement of normal marrow elements with 96% lymphoblasts of FAB L1 morphology that were myeloperoxidase negative. Immunophenotyping studies showed that blasts were positive for CD1 (72%), CD2 (71%), CD3 (92%), CD4 (86%), CD5 (94%), CD7 (98%), CD8 (83%) and TdT (80%). The diagnosis of T-ALL FAB L1 was made.

Physical examination demonstrated spleen enlargement (5 cm below the costal margin) and chest X-ray showed evidence of mediastinal mass. No CNS disease was apparent. Cytogenetic analysis revealed a 46, XX without clonal abnormalities. RT-PCR analysis did not reveal the presence of BCR/ABL, MLL/AF-4 and PML/RARα fusion mRNAs. Due to the shortage of DNA, the clonality was investigated by means of heteroduplex analysis of the amplified T-cell receptor (TcR)γ and (TcR)δ gene recombinations (namely Vγ I-Jγ1.3/2.3, Vγ II-Jγ1.3/2.3 and Vδ1-Jδ1). At conversion, PCR analysis showed a clonal pattern of the TcRδ (Vδ1-Jδ1). After 5 weeks of chemotherapy (prednisone, vincristine, daunorubicin and cyclophosphamide) a CR of the T-ALL was obtained. Remission was further consolidated by three intensification courses according to the L-VAMP protocol. The patient underwent allogenic bone marrow transplantation in April 1996 but died of veno-occlusive disease one month later.

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Table 1. Laboratory features of the patient at diagnosis and at relapse.

	Sept. 1992 diagnosis	*Sept. 1995 relapse*
Morphology (FAB)	AML (M3)	ALL (L1)
Cytochemistry		
PAS	± – –	+ + +
MPO	+ + +	– – –
Immunophenotype		
HLA-DR	0%	28%
CD1	nd	72%
CD2	2%	71%
CD3	0%	92%
CD4	1%	86%
CD5	nd	94%
CD7	0%	98%
CD8	0%	83%
CD13	94%	15%
CD33	99%	3%
CD34	1%	1%
TdT	nd	80%
Cytogenetic analysis	46, XX, t(15;17)	46, XX
Molecular analysis		
PML/RARα	Positive	Negative
BCR/ABL	Negative	Negative
MLL/AF-4	nd	Negative

nd: not done

Discussion

In this report we describe a patient with T-ALL occurring at *relapse* after an initial diagnosis of APL. Recurrent leukemia in APL patients usually reveals the same morphological and cytogenetic features as those found at diagnosis. Two cases with AML of M1 and M2 FAB-subtype have been reported in APL patients at relapse. Both patients had a myelodysplastic syndrome (MDS) after 2-3 years from diagnosis of APL. One patient rapidly developed AML (FAB subtype M2) with an unbalanced, apparently dicentric 5;17 translocation [45, XX, dic(5;17)(q11;p11)] resulting in monosomy for the long arm of chromosome 5 and for the short arm of chromosome 17.[2] In the other patient, AML (FAB subtype M1) was observed after 7 months with a t(7;21)(q31;q22) in all metaphases.[3]

ALL has occasionally been reported as a secondary leukemia both in adults and children.[4-11] The clinical and biological features of nine cases from the literature (including the present case) are summarized in Table 2.

Six of these patients were children (median age: 10.5 yrs), while the median interval from the first to the second diagnosis was 1 year (range: < 1-3 yrs). The FAB type mainly involved monocytic lineage (3 M5 and 3 M4). The therapy, reported in 6/8 cases, included DNA topoisomerase II inhibitors such as anthracyclines, mitoxantrone and epipodophyllotoxin derivate, as in our case. The acute leukemia reported in the literature after treatment with these drugs presented cytogenetic abnormalities with 11q23 involvement;[12] this region may be especially susceptible to therapy-induced mutations. No cytogenetic alterations or evidence of a persisting APL clone or PML/RARα gene rearrangement were found at relapse occurring after a 3-year interval of CR in our patient.

Six reported sALL (four children and two adults) displayed B phenotype. To our knowledge, our patient is the first reported to have developed T-ALL as a secondary leukemia after APL, confirmed by

Table 2. Clinical and laboratory features of reported secondary ALL cases following AML.

No	*1st diagnosis (FAB)*	*Therapy*	*Age/Sex*	*Time from AML (yrs)*	*2nd diagnosis (FAB)*	*Ref.*
1	AML M5	ADR, VCR PRD, ARA-C, EDX	9.2y/M	1.2	°ALL (L1)	4
2	AML M4	DNR, ARA-C, ADR, VP-16, 5-Aza, 6-TG	6y/M	1	ALL (L1) $CD10^+$	5
3	AML M1	DNR, ARA-C, 6-TG, AMSA, VP-16, 5-Aza	40y/M	1	ALL (L1) $CD10^+$	6
4	AML M2	DNR, ARA-C, 6-TG	3y/M	1	°ALL (L1)	7
5	AML M5	NR	4.4y/M	3	ALL (L2) $CD19^+$ CD10-	8
6	AML M5	VM-26, VP-16	1.1y/F	1	ALL (L1) $CD10^+$	9
7	AML M4	DNR, ARA-C, 6-TG, VCR, VP-16, EDX, AMSA, ADR	3.7y/M	2.7	ALL (L1) $CD19^+$ CD10-	10
8	AML M4	NR	47y/?	< 1	ALL (L2) $CD19^+$	11
9	AML M3	IDA, ARA-C, MTZ, VP-16, 6-TG	28y/F	3	T-ALL (L1) $CD2^+$ $CD3^+$	*

*ADR, doxorubicin; VCR, vincristine; PRD, prednisone; ARA-C, cytosine arabinoside; EDX, cyclophosphamide; DNR, daunorubicin; VP-16, etoposide; 5-Aza, azathioprine; 6-TG, thioguanine; AMSA, amsacrine; VM-26, teniposide; IDA, idarubicin; MTZ, mitoxantrone; y: year; NR: not reported; *this report; °immunophenotype not reported.*

modern diagnostic techniques including immunophenotyping and genotyping.

Any attempt to imply a connection between the two events would be purely speculative. We could argue that both leukemias observed in the patient were nothing other than the blast crisis of a chronic myelogenous leukemia (CML), since even APL has rarely been reported in CML patients.[13] However, RT-PCR analysis did not reveal the presence of BCR/ABL fusion transcripts in either BM samples.

Some acute leukemias relapse with a completely different karyotype from their original disease. One explanation for this finding is the development (presentation) of sALL through transformation of the normal lymphoid stem cell.[14] However, in our case, the lack of any identifiable structural chromosome abnormality at relapse suggests that this T-ALL originated from a different clone from that of the APL cells. Surely, this was not a case of acute biphenotypic leukemia.[15]

In conclusion, the occurrence of a secondary, apparently unrelated, leukemia in a patient successfully treated for APL might disclose a genetic susceptibility, similar to that reported in patients who develop recurrent tumors during life.[16] The identification of the genetic mechanism(s) underlying the development of a secondary ALL could have important implications on both preventive and therapeutic patient management.

Contributions and Acknowledgments

VL was responsible for the conception of the study. GS and GP followed the patient clinically. AP contributed to the molecular biology aspect and AM to the phenotypical aspect. AB supervised the molecular biology studies. VL wrote the paper with GS collaboration. All the authors contributed to the critical revision and approval of the final version of paper.

Funding

This work has been supported by AIL "Trenta Ore per la Vita" project and MURST.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received December 4, 1997; accepted February 26, 1998.

References

1. Hunger SP, Sklar J, Link MP. Acute lymphoblastic leukemia occurring as a second malignant neoplasm in childhood: report of three cases and review of the literature. J Clin Oncol 1992; 10:156-63.
2. Hatzis T, Standen GR, Howell RT, Savill C, Wagstaff M, Scott GL. Acute promyelocytic leukemia (M3): relapse with acute myeloblastic leukemia (M2) and dic(5;17)(q11;p11). Am J Hematol 1995; 48:40-4.
3. 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.
4. Emami A, Ravindranath Y, Inoue S, Kaplan J, Lusher JM. Phenotypic change of acute monocytic leukemia to acute lymphoblastic leukemia on therapy. Am J Pediatr Hematol Oncol 1983; 5: 341-3.
5. Stass S, Mirro J, Melvin S, Pui C-H, Murphy SB, Williams D. Lineage switch in acute leukemia. Blood 1984; 64:701-6.
6. Marcus RE, Matutes E, Drysdale H, Catovsky D. Phenotypic conversion of TdT+ adult AML to CALLA+ ALL. Scand J Haematol 1985; 35:343-7.
7. Bernstein ML, Esseltine DW, Emond J, Vekemans M. Acute lymphoblastic leukemia at relapse in a child with acute myeloblastic leukemia. Am J Pediatr Hematol Oncol 1986; 8:153-7.
8. Lampert F, Harbott J, Ludwig W-D et al. Acute leukemia with chromosome translocation (4;11): 7 new patients and analysis of 71 cases. Blut 1987; 54: 325-35.
9. Shimizu H, Culbert SJ, Cork A, Iaucone JI. A lineage switch in acute monocytic leukemia. Am J Pediatr Hematol Oncol 1989; 11:162-6.
10. Hudson MM, Raimondi SC, Behm FG, Pui C-H. Childhood acute leukemia with t(11;19)(q23;p13). Leukemia 1991; 5:1064-8.
11. Lounici A, Cony-Makhoul P, Lacombe F, et al. Acute lymphoblastic leukemia at relapse in an adult with acute myeloid leukemia. Blood 1996; 88(suppl.1): 3391.
12. Pui CH, Frederick GB, Raimondi SC, et al. Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. N Engl J Med 1989; 321:136-42.
13. Wiernik PH, Dutcher JP, Paietta E, et al. Treatment of promyelocytic blast crisis of chronic myelogenous leukemia with all-trans-retinoic acid. Leukemia 1991; 5:504-9.
14. Raimondi SC, Pui C-H, Head DR, Rivera GK, Behm FG. Cytogenetically different leukemic clones at relapse of childhood acute lymphoblastic leukemia. Blood 1993; 82:576-80.
15. Matutes E, Morilla R, Farahat N,et al. Definition of acute biphenotypic leukemia. Haematologica 1997; 82:64-6.
16. Gallagher A, Darley RL, Padua R. The molecular basis of myelodysplastic syndromes. Haematologica 1997; 82:191-204.