Translocation t(1;19)(q23;p13) in Acute Lymphoblastic Leukemia

A Report on Six New Cases and an Unusual t(17;19)(q11;q13), With Special Reference to Prognostic Factors

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ABSTRACT: *We report clinical, immunologic, and cytogenetic characteristics of six patients with a t(1;19)(q23;p13) that was balanced in one case and of the unbalanced type [−19,der (19)t(1;19)(q23;p13)] in the remaining five cases. Intracytoplasmic immunoglobulins (cIg) were positive in the three cases where they were found. We also report on another patient, with a t(17;19) involving 17q11 and probably 19q13 regions, although involvement of 19p13 could not be excluded. In this patient, cIg were also present, thus raising the issue of whether such a rearrangement could be a variant of t(1;19). Clinically, five patients belonged to the high-risk acute lymphoblastic leukemia (ALL) group, because of high leukocytosis, central nervous system (CNS) disease at presentation, or massive organomegaly. Cytologically, all cases were FAB type L1. Except for the two cases allografted in the first complete remission (CR) all patients relapsed, three of them within 13 months. Two CNS relapses were seen in spite of adequate CNS prophylaxis. ALL with t(1;19) appears to be a poor-risk ALL subgroup and probably requires a reinforcement of therapeutic modalities that might include, when possible, allografting at first CR.*

INTRODUCTION

In recent large series of acute lymphoblastic leukemias (ALL), emphasis has been put on the important prognostic value of cytogenetic findings at diagnosis [1–3]. Translocations, such as t(9;22)(q34;q11), t(4;11)(q21;q23), and t(8;14)(q24;q32), in particular, are associated with a short survival [2] and their finding in ALL is now regarded by most authors as an indication for early bone marrow transplantation

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(BMT) in first complete remission (CR) [4]. The t(1;19), which is encountered in 25–35% of pre-B ALL cases, was originally thought to involve 1q23 and 19q13 regions [5–8]. Recently, the use of cell synchronization techniques has shown that the breakpoint on chromosome 19 was located in 19p13.3 [9, 10], thus leading to a t(1;19)(q23;p13.3). Twenty-six cases of ALL with t(1;19) have been reported so far, and controversy on the prognostic value of this finding in ALL still exists. We report seven additional cases of ALL with chromosome 19 abnormalities, six of which had a t(1;19)(q23;p13), whereas one showed probable t(17;19)(q11;q13).

MATERIALS AND METHODS

Chromosomes from bone marrow (BM) or peripheral blood (PB) were studied without stimulation after 24-hour culture in Eagle medium supplemented with 20% calf serum. Chromosome preparations were made according to standard G- or R-banding methods. Karyotypes were described according to the ISCN 1978 [11].

RESULTS

Cytogenetic Findings

Of 200 newly diagnosed ALL patients (excluding Burkitt ALL) studied at our institution between January 1981 and September 1987, R and/or G banding were successful in 174 patients, including 85 children (<15 years) and 89 adults (>15 years). Ninety-two of the patients (53%) were found to have clonal abnormalities. A specific translocation between chromosomes 1 and 19[t(1;19)(q23;p13)] was identified in six patients. A balanced t(1;19) was observed in case 1, associated with chromosome 14 monosomy. In cases, 2, 3, 4, 6, and 7, a pair of normal chromosomes 1 and normal chromosomes 19 were present, and the abnormal chromosome 19 (der19) consisted of most of the other #19 translocated to part of the long arm of chromosome 1 (i.e., −19,+der(19)t(1;19)(q23;p13)) (Fig. 1).

In patient 7, der(19)t(1;19) was associated with del(9)(p21) in 14 cells and 12 normal mitoses.

In patient 5, an unusual balanced t(17;19) was present as the sole anomaly in 42% of the cells and associated with duplication of chromosome X in 58% of the mitoses (BM and PB) (Fig. 2). It involved bands 17q11 and probably 19q13 rather than 19p13, although the latter interpretation cannot be ruled out (Fig. 2). The constitutional karyotype of the patient was normal (25 cells). Complete results of chromosome studies of the seven patients are shown in Table 3.

Clinical, Cytologic, and Immunologic Findings

Initial data are summarized in Tables 1 and 2. There were four males and three females with a mean age of 16.8 years (range 7–26 years). Organomegaly, including splenomegaly, was present in every patient and was massive in two, but no mediastinal enlargement was found. Patient 1 had central nervous system (CNS) disease at presentation. Other risk factors included high leukocytosis ($>100 \times 10^9$/L) in three. Cytologically, all cases were classified as FAB L1 subgroup. Immunologically, blasts were T $(CD_2)^-$, sIg^-, $CALLA^+$, Ia^+ in the six cases studied (Table 2). Cytoplasmic immunoglobulins (cIg) were found in the four patients tested, thus proving their pre-B origin.

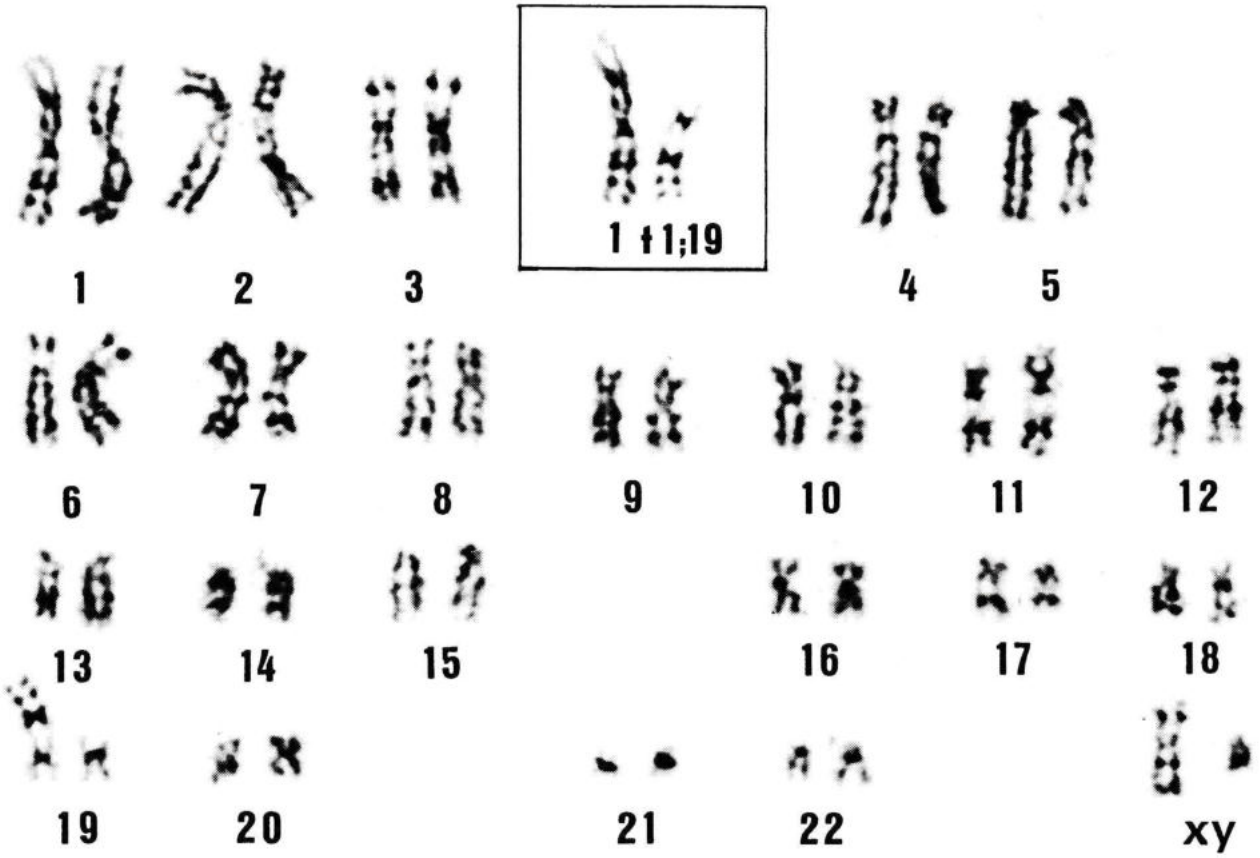

Figure 1 Representative karyotype from case 3: 46,XY,−19,der(19),+t(1;19)(q23;p13) (GTG banded); breakpoints are indicated by arrows.

All patients were treated with the FRALLE 83 protocol [12], which includes daunorubicin in the induction course, CNS disease prophylaxis by intrathecal MTX, and cranial irradiation, three to four intensive consolidation courses, and maintenance therapy for 2 to 3 years. Complete remission was achieved in six patients, but patient 2 died of sepsis during the period of aplasia.

Patients 4 and 7 were allografted early in the first CR and remain in remission 10+ and 58+ months, respectively, after BMT. All the other patients relapsed: three relapsed early at 5, 10, and 13 months, in marrow (case 6), CNS (case 3), and both (case 1), respectively. Patient 5 had a late relapse at 47 months in bone marrow. Patients 1, 3, and 5 obtained a second CR with chemotherapy, and patient 3 was allografted after a second CNS relapse, in the third remission. He remains in CR 10 months after BMT.

DISCUSSION

Among 92 ALL patients with abnormal cytogenetic findings seen at our institution, seven had a structural rearrangement involving chromosome 19, with t(1;19)(q23;p13) in six cases and a probable t(17;19)(p11;q13) in the remaining patient. Patient 7, who has previously been reported [16], had both t(1;19) and del(9)(p21).

In Table 4 the clinical, cytologic, and immunologic data of the 26 previously published cases of ALL with t(1;19) are summarized. Sex and age were reported in 19 cases, nine of whom were males and ten females, with a mean age of 8 years. Clinical findings were detailed in only six patients, and five had organomegaly, a finding that was constant in our series. No mediastinal mass or CNS disease at diagnosis was reported in other series, whereas our patient 1 had initial CNS involvement. The

Table 1 Clinical and hematologic findings in the seven patients at presentation and outcome

Patient	Age/sex	Organo-megaly	Mediastinal enlargement	CNS disease	WBC ($\times 10^9$/L)	Hb (g/dl)	Platelets ($\times 10^9$/L)	FAB type	CR obtained	First CR duration (mo)	Type of relapse	Survival (mo)
1	10/M	Moderate	0	+	26	8.4	92	L1	+	13	Marrow + CNS	31
2	14/F	Moderate	0	0	8.4	10	67	L1	DA	—		1
3	18/M	Moderate	0	0	42	7	48	L1	+	10	CNS	40+[b]
4	18/M	Massive	0	0	31.4	7.5	30	L1	+	14+[a]		15+
5	26/M	Massive	0	0	800	8.5	18	L1	+	47	Marrow	53+
6	7/F	Moderate	0	0	480	11	5	L1	+	5	Marrow	6
7	25/F	Moderate	0	0	150	11	74	L1	+	62+[a]		63+

Abbreviations: CNS, central nervous system; WBC, white blood cell count; Hb, hemoglobin; CR, complete remission; DA, death in aplasia.

[a] Patient allografted in first CR.

[b] Patient allografted in third CR.

Table 2 Immunologic studies in the seven patients

Patients	T(CD_2)	sIg	CALLA	Ia	cIg
1. D.G.	−	−	+	+	+
2. L.C.	−	−	+	+	ND
3. B.P.	−	−	+	+	+
4. R.A.	−	−	+	+	+
5. M.P.	−	−	+	+	+
6. R.R.	−	−	+	+	ND
7. G.D.	ND	ND	ND	ND	ND

Abbreviation: ND, no data.

average leukocyte count was 12 × 10^9/L in one study [6], and seven of the other 14 patients in whom the leukocyte count is available had more than 25 × 10^9/L but only one had more than 100 × 10^9/L. Most published patients therefore appeared to belong to the standard-risk group. In contrast, five of our seven patients belonged to the high-risk group, patients 5, 6, and 7 by means of leukocytosis >100 × 10^9/L, patient 1 because of CNS disease at presentation, and patient 4 because of massive

Figure 2 Five partial karyotypes showing t(17;19)(q11;q13) (RHG and GTG banded) in a case of pre-B ALL.

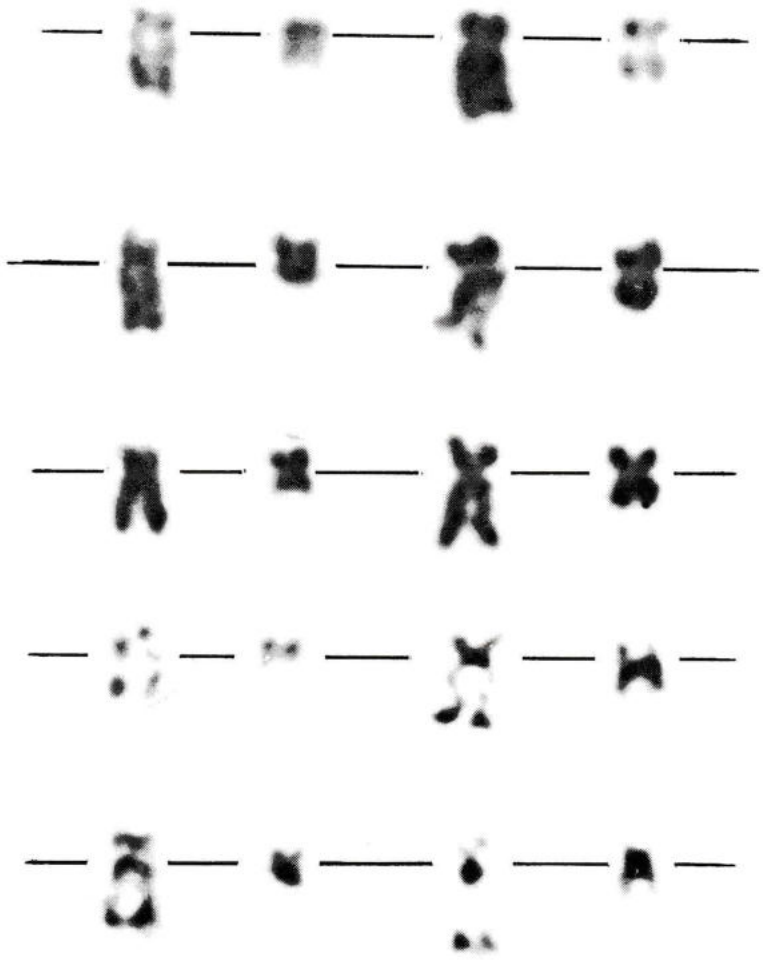

Table 3 Cytogenetic results in the seven patients

Patient	Material	Culture	No. of cells	Normal cells	Abnormal clone[a]
1. D.E.	PB	24 hr	32	26	45,XY,−14,t(1;19)(q23;p13)
2. L.C.	PB	24 hr	20	16	46,XX,−19,+der(19)t(1;19)(q23;p13)
3. B.P.	PB	24 hr	39	31	46,XY,−19,+der(19)t(1;19)(q23;p13)
	BM	24 hr	3	1	46,XY,−19,+der(19)t(1;19)(q23;p13)
4. R.A.	BM	24 hr	31	8	46,XY,−19,+der(19)t(1;19)(q23;p13)
	BM	24 hr	27	27	
5. M.P.	BM	24 hr	8	—	46,XY,t(17;19)(q11;q13) (5) 47,XY,+X,t(17;19)(q11;q13) (3)
	PB	24 hr	23	—	46,X,+X,−Y,t(17;19)(q11;q13) (8) 47,XY,+X,t(17;19)(q11;q13) (15)
	PB + PHA	72 hr	25	25	
6. R.R.	PB	24 hr	11	—	46,XX,−19,+der(19)t(1;19)(q23;p13)
7. G.D.	PB	24 hr	26	12	46,XX,del(9)(p21),−19,+der(19) t(1;19)(q23;p13)

Abbreviations: PB, peripheral blood; BM, bone marrow; PHA, phytohemagglutinin.

[a] The number in parentheses is the number of cells.

Table 4 Review of the literature

Patients	Age/ sex	Organo-megaly	Medias-tinal Mass	CNS disease	WBC (10^9/L)	Morphol-ogy FAB	Immunologic results			
							sIg	T	CALLA	cIg
1	21/M	+	0		3,7	L1	−	−	+	ND
2	30/M	+	0		7,4	L2	−	+	ND	ND
3	8/F	+	0		6,2	L1	−	−	+	ND
4	5/M	0	0		7,4	L1	−	−	+	ND
5	19/F	+	0		4,0	L1	−	−	+	ND
6	2M, 2F, average 11 yr				average 12		−		+	+
7							−		+	+
8							−		+	+
9							−		+	+
10	2,5/F	++	0		24,7	ND	−	−	−	ND
11	2/M					ND	−	−	ND	ND
12	3,5/M				18	L1	−		+	+
13	3/F				49,5	L1	−	−	ND	ND
14						L1			+	+
15						L1			+	+
16						L1			+	+
17						L1			+	+
18						L1			+	+
19						L1			+	+
20						L1			+	+
21	1/F				8,8	L1	−	ND	+	ND
22	9 mo/F				4,0	L1	−	ND	+	+
23	4/M				0,8	L1	−	ND	+	ND
24	16/F				8,0	L2	−	ND	+	ND
25	4/M				3,0	L1	−	−	+	+
26	3/F				4,9	L1	−	−	+	+

organomegaly. Furthermore, four of our patients were aged 18 years or more. Cytologically, all our cases, and all previously reported cases (except two that were L2) [1, 15] could be classified as FAB L1.

Immunologically, in the 15 published patients in which they were searched, cIg were found in every case, showing their pre-B cell origin, whereas another patient had T-cell ALL [5]. In our patients, the pre-B origin [17] was documented in four cases, whereas in the three remaining cases, no search for cIg could be made.

Interestingly, cIg were found in patient 5, who had the t(17;19), thus proving the pre-B origin of this ALL case and raising the issue of whether such a translocation could be a variant of t(1;19)(q23;p13). The fact that 19q13 region seemed involved in this patient argues against the variant hypothesis. However, we could not exclude an involvement of 19p13 rather than 19q13. Nothing is known about the mechanism whereby t(1;19)(q23;p13) contributes to leukemogenesis, but a cellular oncogene, *c-ski*, has been mapped to 1q23 and to the human insulin receptor gene, which has structural homologies with the epidermal growth factor receptor (erb B) to 19p13 [18]. The finding of variant translocations of t(1;19) in pre-B cell ALL, involving 19p13 but not 1q23 would stress the importance of rearrangements of the 19p13 region in this subset of ALL.

Table 4 *Continued*

Karyotype abnormalities	First CR duration (mo)	Ref
47,XY,t(9;22)(q34;q11),t(1;19)(q21;q13),i(7q),+7,8p+	36	[5]
47,XY,t(1;19)(q21;q13),9p+,del(10)(q24),14q+,17p+q+,+21	8	[5]
46,XX,t(1;19)(q21;q23)	7	[5]
55,XY,+t(1;19)(q21;q13)+4,+6,+8,+14,+17,−19,+21,+21,+mar1,+mar2	21+	[5]
46,XX,−19,+t(1;19)(q21;q13)	15+	[5]
46,XY,t(1;19)(q23;q13),−19,+der19,t(1;19)(q23;p13)		[6]
47,XX,t(1;19)(q23;q13)+8	median	[6]
46,XX,−19,der19t(1;19)(q23;q13)	CR 8,5	[6]
47,XY−19,der19t(1;19)(q23;q13)		[6]
46,XX,t(1;19)(q21;q13)t(1;13)(q12;p13),t(13;21)(q13;q21.2)		[7]
47,XY,+8,−19,t(1;19)(q21;q13),inv(5)(q13,q35)		[8]
46,XY,t(1;19)(q23;p13),13q+		[13]
46,XX,t(1;19)(q21;q13)		[14]
46,XY,t(1;19)(q23;p13.3),13q+		[9]
48,XY,+5,+10,−19,der(19)t(1;19)(q23;p13.3)		[9]
45,XX,−20,−19,+der(19)t(1;19)(q23;p13.3),del(8)(q22)		[9]
45,XX,−13,−19,+der(19)t(1;19)(q23;p13.3),del(9)(p13)		[9]
46,XX,14p+,−19,+der(19)t(1;19)(q23;p13.3)		[9]
46,XX,2p+,−19,+der(19)t(1;19)(q23;p13.3)		[9]
46,XY,−19,der(19)t(1;19)(q23;p13.3),i(7q)		[9]
46,XY,inv(9)(p12,q13)/46,XY,−9,−13,+?20,+mar,t(1;19)+mar,t(1;19)(q23;p13.3),inv(9)(p12q13),t(14;?)(q11;?)		[9]
46,XX,t(1;19)(q23;p13)		[15]
46,XX,t(1;19)(q23;p13)		[15]
46,XY,−19,der(19)t(1;19)(q23;p13)		[15]
46,XX,−19,der(19)t(1;19)(q23;p13)		[15]
46,XX,−19,+der(19)t(1;19)(q23;p13)		[15]
46,XX,t(1;19)(q23;p13)/49,XX,+5,+8,+8,t(1;19)(q23;p13/46,XX,−19,+der(19)t(1;19)(q23;p13)		[15]

Among the 32 reported patients with t(1;19) (including our six cases), this translocation was balanced in 16 cases and unbalanced [with −19,der(19)t(1;19)] in 15 patients, whereas the remaining patient had a mosaicism of both types of leukemic cells [15]. No clinical, cytologic, immunologic, or prognostic differences appeared to exist between these two different subgroups.

Although translocations as a whole are associated with a poor prognosis in ALL, the outcome of patients with translocations other than t(8;14),t(9;22) and t(4;11) is not precisely defined. Michael et al. [5] considered that t(1;19) did not carry a poor prognosis, but two of their five patients had an early relapse. Median duration of the first CR was only 34 weeks in the cases reported by Caroll et al. [6], and three of the six patients of Shikano et al. [15] had short remissions. In our series, we observed three early relapses at 5, 10, and 13 months, respectively, and one late relapse at 47 months. In these patients, however, the "impact" of the t(1;19) on the occurrence of early relapse cannot be determined as three of the four had poor prognostic factors (CNS disease at presentation in one 800 and 480 $\times$ 10^9/L leukocytes in the others). Nevertheless, in one series [6], prognosis of the pre-B ALL with t(1;19) was less favorable than that of pre-B ALL, without t(1;19), although the latter had higher leukocyte counts. Accordingly, the two patients of Michael et al. [5] and two of the three patients of Shikano et al. [15] who had early relapses belonged to the standard-risk ALL group. Of note is the fact that we encountered two CNS relapses in spite of adequate CNS prophylaxis. Shikano et al. [15] also reported one case of CNS relapse. Although the number of patients with t(1;19) reported is still small, early relapses after chemotherapy seem to occur frequently. Apart from our three cases, no other reported patient underwent bone marrow transplantation (BMT). Our three allografted patients (two of whom were grafted in first CR) remain in remission, but follow-up is still short in two of them.

Allogeneic BMT in the first CR has clearly improved the prognosis of very high risk ALL, such as ALL with the Philadelphia chromosome [4]. The t(1;19) also appears to be a high-risk factor in ALL, although larger numbers of patients and longer follow-up will be required to ascertain this point. Its presence may require a therapeutic reinforcement. Whether such reinforcement should include allogeneic BMT (when possible) in the first CR will also have to be determined in larger studies.

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