CYTOGENETIC STUDIES IN 30 PATIENTS WITH BURKITT'S LYMPHOMA OR L3 ACUTE LYMPHOBLASTIC LEUKEMIA WITH SPECIAL REFERENCE TO ADDITIONAL CHROMOSOME ABNORMALITIES

J.L. LAI[1], P. FENAUX[2], M. ZANDECKI[3], B. NELKEN[4], J.J. HUART[5], M. DEMINATTI[1]

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SUMMARY : We performed cytogenetic analysis in 23 consecutive patients with Burkitt's ALL and 7 patients with Burkitt's lymphoma. Only one patient had a normal karyotype. Twenty-seven patients had a (8;14) translocation and 2 a (2;8) translocation. No (8;22) translocation was seen. In 12 patients (41 %), the t(8;14) was the only chromosome rearrangement whereas in the 18 remaining cases (59 %), the t(8;14) or t(2;8) was associated with other numerical or structural abnormalities. Chromosomes 1, 7 and 6 were rearranged in 10, 8, and 5 patients, respectively, usually in translocations, duplications, deletions (chromosome 6), or isochromosome of the long arm (chromosomes 1 or 7). The incidence of these additional rearrangements is discussed with regard to previously published reports and the chromosome localization of oncogenes.

KEY-WORDS : Burkitt's lymphoma. — L3 acute lymphoblastic leukemia. — Additional chromosome abnormalities.

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RÉSUMÉ : Vingt-trois patients atteints de LAL (L3) de type Burkitt et 7 patients de lymphome de Burkitt sont étudiés sur le plan cytogénétique. Un seul patient présente un caryotype médullaire normal. Chez les autres patients, on retrouve principalement une translocation (8;14) (27 patients) ou une translocation (2;8) (2 patients). Aucune translocation variante (8;22) n'est retrouvée dans notre série. Chez 12 patients (41 %), la translocation (8;14) est la seule anomalie, chez les autres (59 %), la t(8;14) ou t(2;8) est associée à d'autres anomalies numériques ou structurales. Les chromosomes 1, 7 et 6 sont remaniés respectivement chez 10, 8 et 5 patients, le plus souvent sous forme de translocations, duplications, délétions (chromosome 6) ou sous forme d'isochromosomes des bras longs des chromosomes 1 et 7. La fréquence de ces anomalies est discutée en fonction des données de la littérature et de la localisation de certains oncogènes.

MOTS-CLÉS : Lymphome de Burkitt. — Leucémie aiguë lymphoblastique (L3). — Anomalies chromosomiques surnuméraires.

INTRODUCTION

The occurrence of translocation (8;14)(q24;q32) (Berger et al., 1979) or its variants t(2;8)(p11;q24) (Rowley et al., 1981) and t(8;22)(q24;q11) in Burkitt's lymphoma (BL) and Burkitt's acute lymphoblastic leukemia L_3 ALL is well recognized and se-

1. *Service de Génétique, Faculté de Médecine, 1, place de Verdun, 59045 LILLE Cedex (France).*
2. *Service des Maladies du Sang, CHU.*
3. *Service d'Hématologie,*
4. *Service de Pédiatrie A,*
Hôpital Calmette, av. du Pr J. Leclercq, 59000 LILLE.
5. *Centre Régional de transfusion sanguine, 21, rue Camille-Guérin, 59012 LILLE.*

veral series of patients have been reported (Berger et al., 1979 ; Berger et al., 1982 ; Third international Workshop 1980 ; Van den Berghe et al., 1979). Some patients belonging to these series, and other reported individual cases of BL or L_3 ALL (Knuutila et al., 1983 ; Berger et al., 1982 ; Prieto et al., 1985 ; Douglas et al., 1983 ; Avantin et al., 1987) display numerical and/or structural chromosomal abnormalities in addition to the characteristic translocation involving the 8q24 region.

In this work, we analyzed the frequency and features of these additional cytogenetic findings in 30 cases of BL or L_3 ALL diagnosed consecutively in our institution.

PATIENTS, MATERIAL AND METHODS

Patients

Between January 1981 and April 1988, diagnosis of BL was made in 7 cases and diagnosis of L_3 ALL in 23.

Twenty-four patients originated from the North of France, three (cases 13, 25, 27) from Northern Africa, and three from Poland (cases 2, 7, 19). Apart from the cytological features of blasts (L_3 in the FAB classification), criteria for the diagnosis of L_3 ALL included bone marrow infiltration by > 50 % blasts in the absence of massive tumor. In two cases (cases 16, 17), which have been previously published (Zandecki et al., 1987), L_3 ALL occurred after chemo- and radiotherapy for Hodgkin's disease (HD). Cases 1-4 have also been previously reported (Laï et al., 1983).

Cytogenetic analysis

Cytogenetic analysis was performed at diagnosis in all cases. Three patients were reexamined at relapse (cases 3, 5, 21). Cytogenetic studies were generally performed on bone marrow (BM), with or without 24-hour culture and on a 24-hour culture of leukocytes isolated by the Dextran Method, without stimulation by PHA. In cases of BL, lymph nodes (LN) or tumor cells (T) were gently cut with a scalpel in Eagle medium and the cell suspension was cultivated without mitogens for 24 hours.

BM, PB, LN, T, pleural or ascite fluid (PF or AF) were then studied cytogenetically. Chromosomes were identified by heating (Dutrillaux and Lejeune, 1971), RHG bands, or trypsin technique (Seabright, 1971) GTG bands.

Surface marker analysis

Surface immunoglobulins (sIg) were analyzed by indirect immunofluorescence in 27 patients with a polyspecific anti-immunoglobulin serum. In 8 patients, the specificity of sIg was studied with anti-μ, γ, α and anti-λ and κ antisera.

RESULTS

Clinical and hematological features of the 23 cases of L_3 ALL and 7 cases of BL are shown in table I. Males predominated both in L_3 ALL (M/F : 19/4) and BL (M/F : 5/2). Median age was 29 in L_3 ALL (range 5-66) and 12 in BL (range 2-36). 12/23 (52 %) L_3 ALL patients reached complete remission (CR) with combination chemotherapy. 7/12 remain in CR after 4+ to 32+ months and 5 relapsed 1 to 7 months after entering CR. 5/7 of the BL cases reached CR and only one has relapsed so far, after 6 months.

Cytogenetic analysis was successful in all 30 patients. Results are shown in tables II and III. A t(8;14)(q24;q32) was found in 27 cases (93 %), a t(2;8)(p11;q24) in 2 cases (15 and 27) but no patient had a t(8;22)(q24;q11). The remaining patient (case n° 23) had a normal karyotype, although 13 mitoses were analyzed (GTG bands).

In 12 patients (41 %), the t(8;14)(q24;q32) was the only chromosome abnormality (cases 1, 2, 4, 7, 9, 10, 16, 18, 19, 21, 28, 29). The 17 (59 %) other patients (including the 2 cases with variant t(2;8)) had additional numerical or structural changes, which mainly involved chromosomes 1, 6 and 7 (table IV).

The long arm of chromosome 1 was involved in 10 patients (33 %). Main rearrangements consisted of partial trisomy (duplication) (fig. 1) or tetrasomy (i(1q)). A preferential association was seen with chromosome 7 (three t(1;7), of which 2 involved (fig. 2 and 3). In one patient (case n° 11), chromosome 1 was involved in a complex structural rearrangement with chromosomes 8 and 14. The 14q+ , in this patient, was due to the addition, on chromosome 14, of a large part of the long arm of chromosome 1 (fig. 3).

Chromosome 7 was rearranged in 8 cases, in a t(1;7) (3 cases ; fig. 2) an i(7q) (3 cases ; fig. 1), a trisomy 7, a del (7)p(11) or a t(4;7)(p21;p22) (fig. 3).

Chromosome 6 was involved in 5 cases, including 3 partial deletions of the long arm (del6q) (fig. 3), one trisomy 6 and one t(1;6)(q25;q22). Four cases of trisomy 12 were seen. Other chromosomes were less often involved : an 11q+ (probably due to duplication) (fig. 3) was seen in 2 cases ; structural abnormalities of chromosome 13 (13q+) or 17 (17p+) were seen in one case each. Finally, marker chromosomes (mar) due to complex structural rearrangements were seen in 3 BL cases but no case of L_3 ALL.

The incidence of abnormalities of chromosome 6 was higher in BL (4/7) than in L_3 ALL (1/23) but other chromosomes appeared equally involved in L_3 ALL and BL. Clinical, hematological features and outcome of patients was not different in patients with t(8;14) or t(2;8) only and in patients with extra

TABLE I

I) Burkitt's ALL.
Initial findings in 30 patients with Burkitt's ALL or lymphoma.

Patient	Sex	Age	Splenomegaly	Lymph nodes	Other tumor site	CNS disease	Leukocytes ($\times 10^9$/L)	Circulating blasts (%)	BM blasts (%)	sIg	FAB type	CR obtention (months)	CR duration (months)	Survival (months)
1	F	15	+	+	–	+	49	73	100	+	L3	–		0.1
2	M	31	+	–	–	+	34	38	94	+	L3	–		2
3	M	5	+	+	–	+	50	65	85	+	L3	+	1	3
4	F	55	+	+	–	–	27	16	96	+	L3	–		0,1
5	M	21	+	+	–	+	8.6	21	95	+	L3	+	7	10
6	F	39	+	+	–	–	40	64	78	+	L3	–		0.5
7	M	32	+	+	–	–	34	21	93	+	L3	–		1
8	M	15	–	+	–	+	48	25	84	+	L3	–		0.5
9	M	21	+	+	–	+	29	57	75	+	L3	+	15	16
10	M	16	+	+	–	+	16	2	76	+	L3	+	1.5	11
11	M	17	–	–	–	+	14	6	94	ND	L3	+	32^+	33^+
12	M	39	–	+	–	–	11.4	1	79	+	L3	Lost to follow up		
13	M	9	–	+	Epidural	–	15	0	90	+	L3	+	26^+	30^+
14	F	25	–	–	–	+	24	5	55	+	L3	+	4^+	30^+
15	M	31	–	–	Pleural	+	8	0	68	+	L3	–		0.1
16	M	41	–	–	–	–	10.2	1	51	+	L3	–		0.5
17	M	41	–	–	–	+	8.8	8	53	+	L3	+	5	6
18	M	42	–	–	–	+	14	12	80	+	L3	+	20^+	21^+
19	M	20	–	–	–	+	51	35	81	+	L3	–		0.1
20	M	66	–	–	–	+	89	60	92	+	L3	+		0.5
21	M	27	–	+	–	+	9.1	1	86	+	L3	+	5.5	7
22	M	18	+	+	Mandibular	+	15	4	85	+	L3	+	3^+	4^+
23	M	38	+	+	Gastric	+	10	5	56	+	L3	+	12^+	14^+

II) Burkitt's lymphoma.
Initial findings in 30 patients with Burkitt's ALL or lymphoma.

Patient	Sex	Age (years)	Clinical presentation	CNS disease	BM blasts %	sIg	CR obtention	CR duration	Survival (months)
24	M	13	Axillary lymph nodes	–	0	+	+	6	10
25	M	15	Abdominal tumor	–	0	+	–	–	1
26	M	2 1/2	Tonsil	–	0	ND	+	60^+	65^+
27	M	4	Abdominal tumor mass	–	0	+	+	40^+	44^+
28	F	5 1/2	Mandibular	–	0	+	+	5^+	6^+
29	M	7	Abdominal mass epidural in filtration	–	0	+	+	4^+	5^+
30	F	36	CNS and marrow involvement	+	100	ND	–	–	1

ND : not determined.

TABLE II. — **Cytogenetic data in 23 patients with ALL_3.**

Patient	Material studies	Karyotype
1	BM (24^H)	46,XX = 2/46, XX,t(8;14) (q24q32) = 29
2	PB (24^H)	46,XY = 15/46, XY,t(8;14) (q24;q32) = 13
3	BM (24^H)	46,XY = 15/46, XY,t(8;14) (q24;q32) = 10/46, XY,t(8;14) (q24q32), −7+t(?1;7 (?q25;q22) = 10/47, XY,t(8;14) (q24;q32), +i(7q) = 8
	PB (24^H) Relapse	46,XY,t(8;14) (q24;q32) = 4/47, XY,t(8;14), +i(7q) = 28
4	BM (24^H)	46,XX = 6/46, XX,t(8;14) (q24;q32) = 3
5	BM (24^H)	46,XY = 5/46, XY,t(8;14) (q24;q32), dup(1) (q21q32) = 12 Fig (1)
	BM (24^H)	46,XY = 2/47, XY+7, t(8;14) (q24;q32), dup(1) (q21q32) = 5
	Relapse	48,XY, +7, +8, t(8;14) (q24;q32), dup(1) (q21q32) = 12
6	BM (24^H)	46,XX,t(8;14) (q24;q32) = 4/46, XX,t(8;14) (q24;q32), del(9) (q12q21) = 13
7	BM (24^H)	46,XY,t(8;14) (q24;q32) = 24
8	PB (24^H)	46,XY = 1/46, XY,t(8;14) (q24;q32) = 16/46, XY,t(8;14) (q24;q32),t(1;7) (q21;p15) = 7 Fig (2)
9	PB (d)	46,XY = 4/46, XY,t(8;14) (q24;q32) = 19
10	BM (d)	46,XY = 1/46, XY,t(8;14) (q24;q32) = 13
11	BM (d)	46,XY = 1/46, XY−14, t(1;14) (q11;q32), del (8) (q24) = 23 Fig (3)
12	BM (d)	47,XY,+12, t(8;14) (q24;q32) = 14/47, XY,+12, t(8;14) (q24;q32) 13q$^+$ = 4
13	BM (d)	46,XY = 9/46, XY,t(8;14) (q24;q32) = 5/46, XY,t(8;14) (q24;q32), dup(1) (q21q25) = 4 Fig. (1)
14	BM (24^H)	46,XX = 2/46, XX,t(8;14) (q24;q32) = 9/46, XX,t(8;14) (q24;q32), del(2) (p12p16) = 6 46,XX,t(8;14) (q24;q32), dup(1) (q32q44) = 4 Fig (1)
15	BM (24^H)	46,XY = 1/47, +12, t(2;8) (p11;q24), 11q+ = 18
16	BM (24^H)	46,XY = 6/46, XY, −7, +mar = 18/46, XY,t(8;14) (q24;q32) = 34
17	BM (24^H)	46,XY = 12/46, XY,t(8;14) (q24;q32) = 35/47, XY,+12,t(8;14) (q24;q32) = 1 47,XY,+i (1q), t(8;14) (q24;q32) = 3 Fig (1)
	PB (24^H)	46,XY = 3
18	BM (d)	46,XY = 1/46, XY,t(8;14) (q24;q32) = 11
	PB (24^H)	46,XY = 1/46, XY,t(8;14) (q24;q32) = 10
19	PB (d)	46,XY,t(8;14) (q24;q32) = 17
20	PB (d) (24^H)	46,XY,t(8;14) (q24;q32) = 2/47, XY,t(8;14) (q24;q32),+i(7q) = 15 Fig (2)
21	BM (24 ^{H})	46,XY = 3
	BM (24^H) Relapse	46,XY,t(8;14) (q24;q32) = 17
22	BM (24^H)	46,XY = 22/46, XY−3,−7, +mar, der7 t(1;7) (q21;q35), del(6) (q14q21), t(8;14) (q24;q32) = 15 Fig (3)
23	BM (24^H)	46,XY = 13

d : direct without 24 hour culture.

chromosome abnormalities. In the L_3 ALL patients, 5/10 with t(8;14) or t(2;8) as the only abnormality reached CR and 3/5 remain in CR, vs 7/13 and 4/7 of the patients with extra chromosome abnormalities.

In BL, the number of patients was too small to draw any conclusion.

DISCUSSION

One of the characteristic translocations of L_3 ALL or BL was found in 29 of our 30 patients, the remaining case having a normal karyotype. The t(8;14)(q24;q32) largely predominated as it was found in 27 cases. In one of these patients, the translocation was unusual, involving the long arm of chromosome 1 in a complex rearrangement. A few other examples of complex translocations, also involving chromosome 1, had previously been published in L_3 ALL and BL (Berger et al., 1982 ; Tanzer et al., 1980).

Only 2 of our patients had the t(2;8)(p11;q24) variant translocation. This incidence (6,6 %) is lower than the 6/26 (23 %) reported by Berger et al., in 1982 and the 8/18 (44 %) reported by Douglass et al. Knuutila et al., however, also encoutered a low incidence of t(2;8)(2/15, 14 %). They found no t(8;22), as in our series, whereas Berger et al. and

TABLE III. — **Cytogenetic data of 7 patients with Burkitt's syndrome.**

Patient	Material studies	Karyotype
24	BM	46,XY = 5/46, XYt(8;14) (q24;q32) = 1/47, XY,+mar, t(8;14) (q24;q32) = 22
25	PF	47,XY,+12,t(8;14) (q24;q32) = 12/48, XY, +12,+mar, t(8;14) (q24;q32) = 2
26	LN	46,XY,t(8;14) (q24;q32) = 9/46, XY,t(8;14) (q24;q32), dup(1) (q21;q32) = 7 (Fig. (2) 46,XY,t(8;14) (q24;q32), −6,+t(1;6) (q11;q14) = 3 Fig (2) 48,XY,t(8;14) (q24;q32), +6,+del(7) (p11) = 1
27	T	46,XY, del(6) (q16;q23), t(2;8) (p11;q24) = 27 Fig (3)
28	LN	46,XY, t(8;14) (q24;q32) = 17
29	AF	46,XY, t(8;14) (q24;q32) = 5
30	BM	45,X(−X),t(8;14) (q24;q32),del(6) (q15;q22),−7,+t(4;7) (q21;p22) 11q+ = 20 Fig (3) 45,X(−X),t(8;14) (q24;q32),del(6) (q15;q22), 17p+ = 5

LN : lymph node ; BM : bone marrow ; PB : peripheral blood ; AF : ascite fluid ; T : tumor without mitogenic stimulation ; PF : pleural fluid.

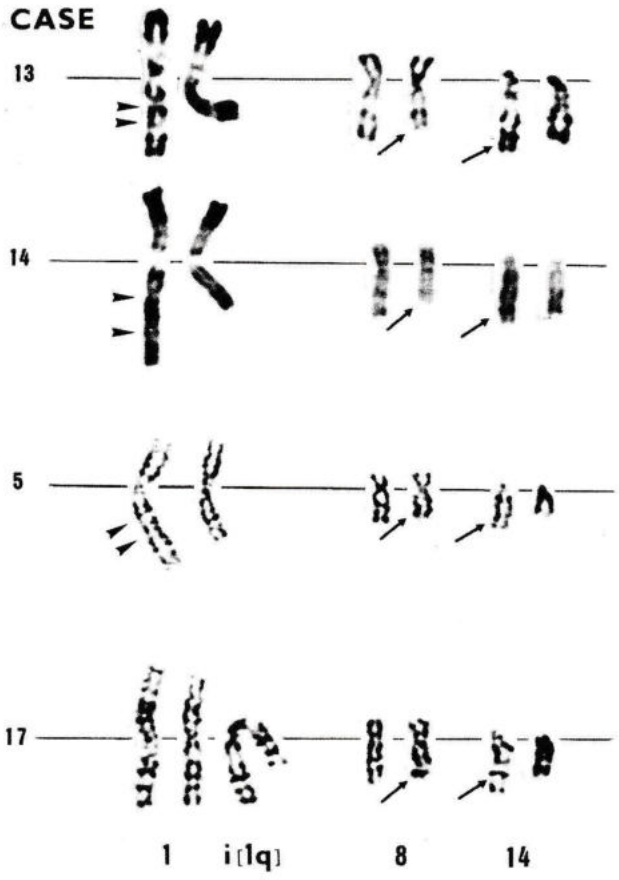

Fig. 1. — Partial karyotype showing t(8;14)(q24;q32) associated with many different structural abnormalities of chromosome 1. Case 13 : dup(1)(q21;q25) (RHG) ; case 14 : dup(1) (q32;q44) (RHG) ; case 5 : dup(1)(q21q32) (GTG) ; case 17 : +i(1q) (GTC).

TABLE IV. — **Chromosome rearrangements in addition to t(8;14) or t(2;8).**

Structural and numeric abnormalities of chromosome	Frequence (%)	Cas n°	Cytogenetic abnormality	Ref with abnormalities
1	10/30 (30)	5-26	dup(1) (q21q32)	4, 10, 15, 18, 24, 29
		13	dup(1) (q21q25)	10
		14	dup(1) q32q44)	4
		3	t(?1;7) (?q25;p22)	24
		8	t(1;7) (q21;p15)	
		22	t(1;7) (q21;q35)	
		17	i(1q)	
		26	t(1;6) (q11;q14)	
		11	t(1;14) (q11q32)	26
7	8/30 (26,6)	8	t(1;7) (q21;p15)	
		22	t(1;7) (q21;q35)	
		3	t(?1;7) (?q25;p22)	24
		5	+ 7	10, 15
		3-20	+ i (7q)	16
		26	del(7)(p11)	
		30	t(4;7) (q21;p22)	
6	5/30 (17)	22	del6 (q14;q21)	10
		27	del6 (q16;q23)	
		30	del6 (q15;q22)	
		26	+ 6	10
		26	t(1;6) (q11;q14)	4
12	4/30 (13,2)	12-15 17-25	+ 12	6, 25
11	2/30 (6,6)	15-30	11q+	10, 15
13	1/30 (3,3)	12	13q+	4, 15
17	1/30 (3,3)		17p+	15

Douglass et al. reported this variant in 4/26 and 0/18 patients, respectively. The t(8;22) was also seen in 3/13 Burkitt's lymphoma or leukemia associated with the acquired immunodeficiency syndrome (Bernheim and Berger, 1988).

One of our patients had a normal karyotype, although 13 mitoses were examined. The absence of a t(8;14) or variant translocations is rare in L_3 ALL or

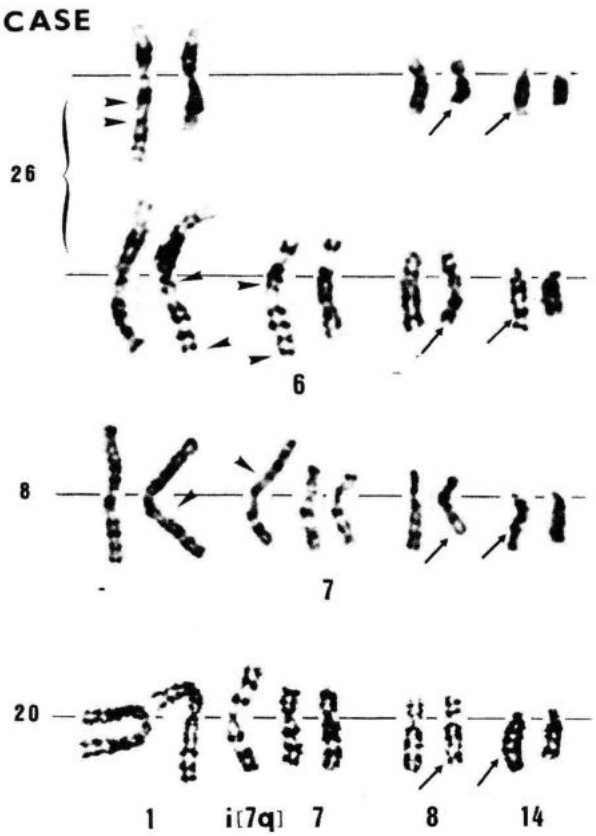

Fig. 2. — Partial karyotype showing t(8;14)(q24;q32) associated with structural abnormalities of chromosomes 1, 6 and 7. Case 26 : dup(1)(q21;q32) and t(1;6)(q11;q14) (GTG) ; case 8 : +t(1;7)(q21;p15) (GTG) ; case 20 : +t(7q) (GTG).

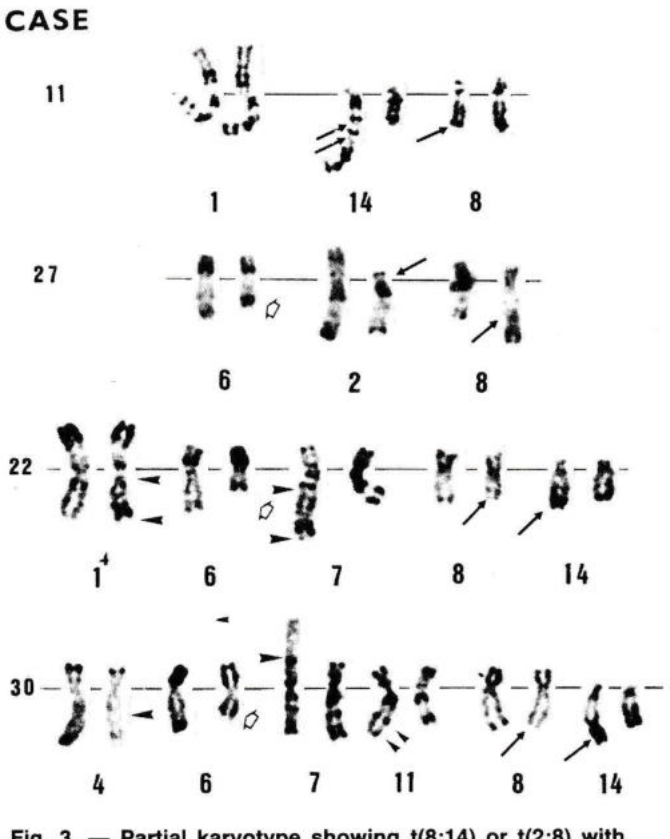

Fig. 3. — Partial karyotype showing t(8;14) or t(2;8) with structural abnormalities of chromosomes 1, 6 and 11. Case 11 : 46,XY,−14,+t(1;?8;14)(q21;q24;q32) (GTG) ; case 27 : t(2;8)(p11;q24) and del(6q) RHG) ; case 22 : del(6q),−7, +t(1;7)(q21;q35) (RHG) ; case 30 : del(6q),+t(4;7)(q21;p22), 11q+ (RHG). White arrows show the del(6q).

BL, as it occurred in none of the patients of Berger et al., and only one of those of Knuutila et al. Most of these patients, however, had cytogenetic abnormalities involving other chromosomes than chromosomes 2, 8, 14, 22 (Berger et al., 1985). In our review of the literature, we found a completely normal karyotype, in L_3 ALL or BL, in two cases only (Douglass et al., 1982 ; Knuutila et al., 1983).

Chromosome rearrangements in addition to t(8;14) or t(2;8) were seen in 17/29 of our patients (58 %). This proportion of additional abnormalities ranged from 52 % to 75 % in previously published series (Berger and Bernheim, 1982 ; Knuutila et al., 1983).

Chromosome 1 was the most frequently involved chromosome in our series, followed by chromosomes 7 and 6, as in previous reports (Knuutila et al., 1983 ; Berger et al., 1982 ; Douglass et al., 1980 ; Miyoshi et al., 1981 ; Whang Peng et al., 1984). This high incidence of abnormalities of chromosome 1 is also found in other blood malignancies, particularly ALL with pre-B phenotype (Carroll et al., 1984 ; Michael et al., 1984), or myeloproliferative disorders (Garhton et al., 1978 ; Rowley, 1978) and in solid tumors (Cerventes et al., 1988).

Rearrangements of chromosome 1 usually consisted, both in our patients and in the literature (table IV), of a duplication of region 1q21q32, 1q21q25, 1q32q44, leading to partial trisomy 1q.

Abnormalities of chromosome 6, in our patients and in other reports on L_3 ALL and BL (Berger et al., 1982 ; Douglass et al., 1980) usually included interstitial deletions of 6q. In addition to our own cases, one patient with trisomy 6 (Douglass et al., 1980) and one with translocation (1;6)(q25;q22) have been reported (Berger et al., 1982).

The most common rearrangement of chromosome 7 in our experience was a t(1;7), preferentially involving 7p. These rearrangements were also frequently encountered by other authors (Knuutila et al., 1983 ; Slater et al., 1982 ; Rowley, 1977). Trisomy 7, as in our case 5, has been reported in a few patients (Knuutila et al., 1983 ; Douglass et al., 1980). However, no case of isochromosome 7q had been previously published.

Finally, additional abnormalities less commonly found in our patients had also been reported in a

few cases : 11q+ (Knuutila et al., 1983 ; Douglass et al., 1980), 13q+ (Berger et al., 1982), trisomy 12 (Tantravahi et al., 1983), and 17p+ (Knuutila et al., 1983). Additional chromosomal rearrangements were also seen in our two patients with L_3 ALL following HD (cases 16 and 17). Recently, Zollino et al. (1988) reported another patient with L_3 ALL following HD. Partial duplication of chromosome 1q in peripheral blood cells had been found 2 years before the onset of L_3 ALL. This finding raises the possibility, that at least in some cases, a chromosome abnormality may preceede the t(8;14) in L_3 ALL.

In our series and in the literature the presence of chromosome changes in addition to t(8;14) or its variants was not associated with any specific clinical, hematological, or prognostic features.

The t(8;14) and its variants seem to be implicated in the pathogenesis of L_3 ALL and BL by means of rearrangements of the c-myc protooncogene (Croce and Nowell, 1985) although the precise mechanism of leukemogenesis still has to be elucidated. Chromosome rearrangements associated to this translocation are usually regarded as secondary (Zandecki et al., 1987) although, as previously seen, they are encountered occasionally in L_3 ALL or BL without t(8;14) (Berger et al., 1985). The chromosome breakpoints involved in the most frequent « secondary » chromosome changes contain several protooncogenes : c-ski in 1q23 ; c-syr and c-ros in 6q21 and 22 ; c-myb in 6q23 (Hecht, 1988). Furthermore, c-ral and c-ara F2 are located on 7p (Hecht, 1988). The role of these oncogenes in the progression or, in some cases, in earlier steps of the disease, will have to be determined.

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