Acute Lymphocytic Leukemia with 9p Anomalies

A Report of Four Additional Cases and Review of the Literature

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ABSTRACT: *Childhood acute lymphocytic leukemia (ALL) with partial deletion of the short arm of chromosome 9 (9p−), particularly in the p21–22 region, associated with bulky disease, has been regarded as a possible subgroup of ALL. We have reviewed clinical and cytologic data in 128 cases of ALL (childhood and adult). Four of them had 9p anomalies. Two patients had a deletion in the 9p21 region associated with another deletion (9p13→pter) in one case and with t(1;19)(q21;p13) in the second patient. A third patient had a t(9;14)(p21;q12) balanced translocation associated with 14q22→qter deletion; the last patient showed a t(5;9)(p14;q21) unbalanced translocation also associated with 14q deletion. All four patients had lymphomatous ALL, but immunophenotype was non-T, in the four cases, (non-T, non-B in two patients and common ALL in the two remaining cases). Acute lymphocytic leukemia with 9p anomalies appears relatively frequently and is usually associated with poor prognostic features (i.e., bulk disease and high leukocyte counts) but does not seem restricted to childhood and T-cell lineage.*

INTRODUCTION

In 1983, Kowalczyk and Sandberg [1] reported on seven cases of childhood acute lymphocytic leukemia (ALL) with partial deletion of the short arm of chromosome 9 (9p−) in the p21–22 region or complete loss of this chromosome. These patients were characterized by older age at diagnosis, lymphomatous features (i.e., prominent lymphadenopathy, mediastinal enlargement, splenomegaly), high white blood cell (WBC) count, T-cell origin in most cases, and accounted for 10% of cases of childhood ALL [1]. The association between lymphomatous ALL, T-cell phenotype, and 9p− was later on confirmed by Chilcote et al. [2], but a recent report by Carroll et al. [3], in contrast, found no correlation between 9p− deletion and either bulky disease or T-cell phenotype in childhood ALL. We have performed cytogenetic studies in 128 cases of ALL and found four patients with balanced or unbalanced

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Table 1 Clinical characteristics and response to therapy in the four patients

Patient	Age/Sex	Lymph nodes[a]	Spleen size[b]	Mediastinal mass	Other organomegaly	Remission/ survival (mo)	Current status
1	11/M	3	3	–	Hepatomegaly	0/6	Alive but progression of the disease
2	36/M	0	0	+	Hepatomegaly enlarged kidneys	4/4+	NED
3	36/M	2	0	–	–	30/30+	NED
4	26/F	2	2	–	–	49/49+	NED

Abbreviation: NED, no evidence of disease.

[a]Lymph node: 0 = not palpable; 1 = palpable but < 1 cm; 2 = 1 to 3 cm; 3 = > 3 cm for a single node or > 5 cm for matted nodes.

[b]Spleen size: 0 = not palpable; 1 = palpable but < 3 cm; 2 = > 3 cm but not below the umbilicum; 3 = below the umbilicum.

chromosome abnormalities involving the short arm of #9: single 9p− deletion in two cases, t(5;9)(p14;q21) in the third case, and t(9;14)(p21;q12) associated with 14q−(q22→q24) in the remaining patient. Clinical and immunologic features of these patients were analyzed and compared with those of the literature.

CASE REPORTS

Clinical Features

Clinical features in the four patients are summarized in Table 1. There were three males and one female and their age ranged from 11 to 36 years. All patients had bulky disease with prominent lymphadenopathy (three cases) and splenomegaly (two cases), but a mediastinal mass was present in one case only. No patient presented with central nervous system or testicular disease. Complete remission (CR) was obtained in three cases (patients 2, 3, and 4), all of whom remain in first CR at 4+, 30+, and 49+ months, respectively. Patient 2 was autografted and patient 4 allografted.

Hematologic Findings

Hematologic and immunologic features are summarized in Table 2. Two patients had no or only slight anemia (hemoglobin > 10 g/dl). All four cases had leucocyte count above 50×10^9/L(range 52–600) and thrombocytopenia. Cytologically, cases 1 and 2 were L–1 in the FAB classification, case 3 was L–2, and case 4 remained unclassified ALL. Cell surface marker analysis revealed Ia and CALLA antigen positivity in cases 1 and 3. All patients were T (CD 2) and B (CD 19) negative.

CYTOGENETIC STUDIES

Cytogenetic studies were performed after 24-hour culture without stimulation by mitogens from bone marrow (BM) (patients 1–3) and peripheral blood (PB) (patients 3 and 4). Staining methods used were RHG- and GTG-banding by heating [4] and trypsin technique [5]. Chromosomal abnormalities were described according to the ISCN [6]. Cytogenetic results of the four patients are recorded in Table 3. Chromosome analysis of RHG- and GTG-banded BM metaphases from patient 1 revealed a t(9;14)(p21;q12) balanced translocation in 100% of metaphase cells and in, respectively, 9–38% during relapse; a deletion near the 14q22-q24 region (Fig. 1a, b) was also observed in that patient. Patient 2 had a modal number of 45 and the karyotype revealed a t(5;9)(p14;q21) unbalanced translocation associated with a 14q deletion as in patient 1. The t(5;9)(p14;q21) was associated with the loss of the 9q21→pter segment including the centromere of #9 (Fig. 2). For patient 3, cytogenetic analysis revealed two 9p deletions, in 9p13 and 9p21 bands, respectively (Fig. 3a). Finally, in patient 4 a del(9)(p21) was seen, in association with a der(19)t(1;19)(q21;p13) (Fig. 3b).

DISCUSSION

Since 1981, we have studied cytogenetically 128 newly diagnosed or relapsed ALL patients (excluding B-ALL cases). In 70 patients (55%), a clonal chromosome anomaly was discovered. Three of these patients had a partial loss of the short arm of chromosome 9 (9p−), and one case had a 9p translocation. The loss of the short arm of chromosome 9 was due to an unbalanced translocation in one case and to a

Table 2 Hematologic and immunologic findings in the four patients with 9p abnormalities

Patients	Hemoglobin (g/dl)	Platelets ($\times 10^9$/L)	WBC ($\times 10^9$L)	Blasts (%)	Blasts in marrow (%)	FAB classification	CALLA	ıa-like	T	B
1	8.5	97	600	98	99	L-1	+	+	–	–
2	13.1	60	52	67	84	L-1	–	–	–	–
3	6	24	64.7	97	94	L-2	+	+	–	–
4	11	74	150	91	—	Not classified	–	–	–	–

Table 3 Cytogenetics of the four patients

Patient	Material/ leukemic state	Metaphase cells (*n*)	Abnormal cells (%)	Karyotype in leukemic cells
1	BM Dg	18	100	46,XY, – 9, + der(9)t(9;14)(p21;q12),del(14)(q22q24)
	BM 1st relapse	58	9	
	BM 2nd relapse	18	38	
2	BM Dg	18	100	45,XY, – 5, – 9, + der(5)t(5;9)(p14;q21),del(14)(q22q24)
3	BM Dg	10	100	46,XY,del(9)(p13),del(9)(p21)
	PB Dg	13	100	46,XY,del(9)(p13),del(9)(p21)
4	PB Dg	26	45	46,XX, – 19,del(9)(p21), + der(19)t(1;19)(q21;p13)

Abbreviation: Dg, at diagnosis.

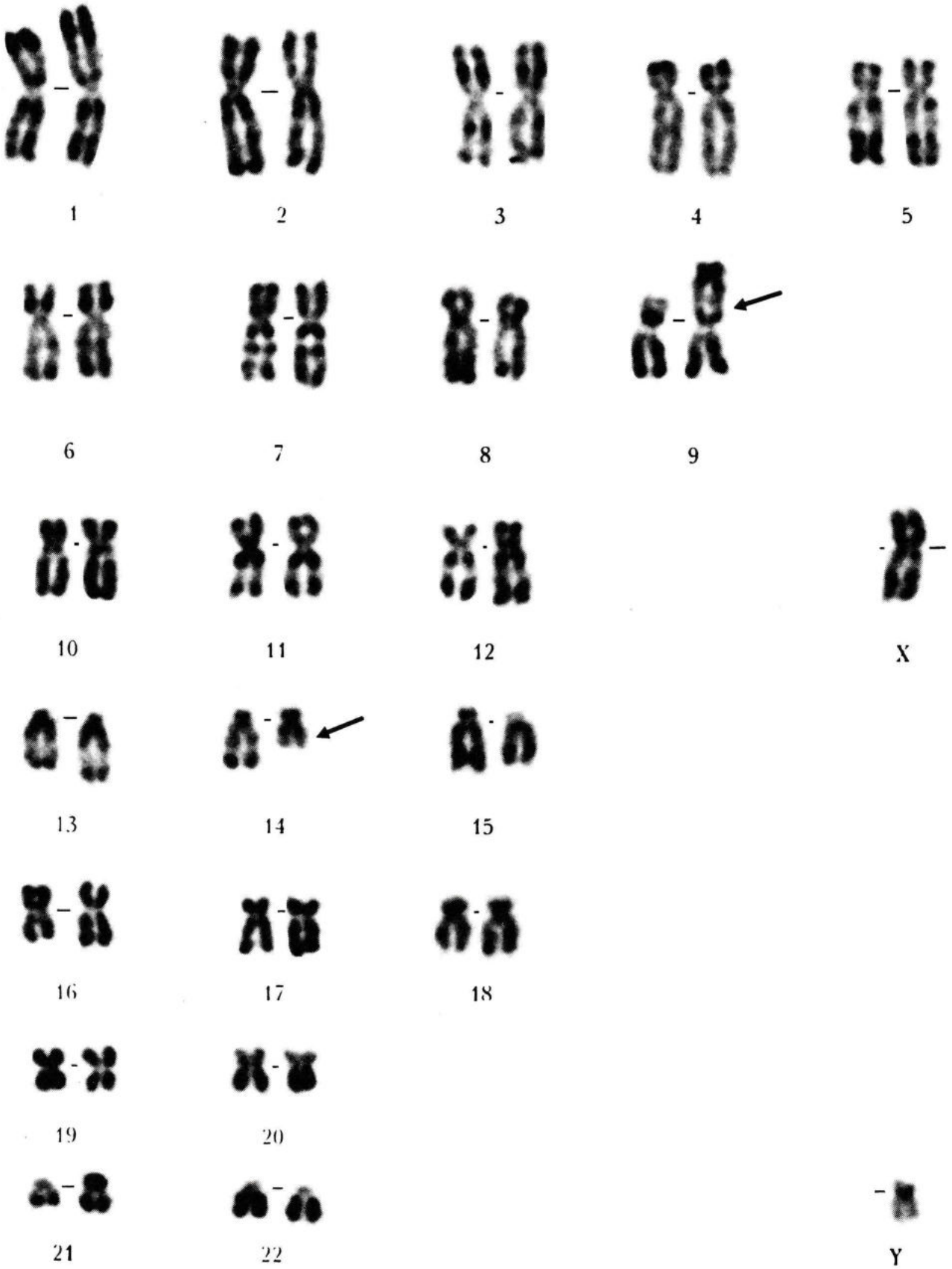


Figure 1 (a) Complete karyotype of patient 1 (RHG bands).

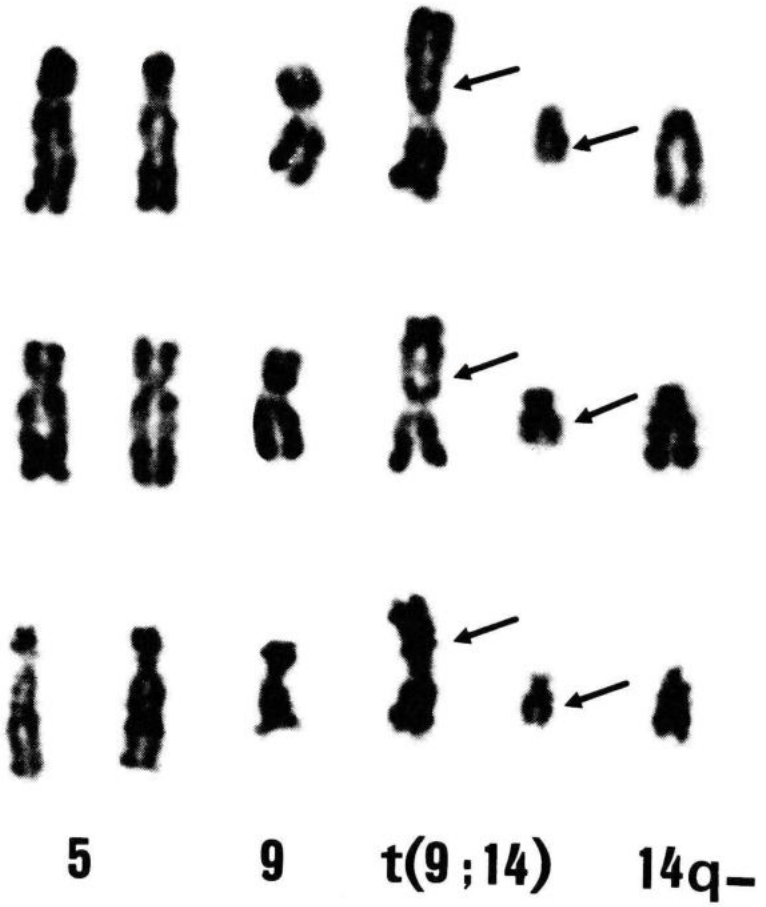
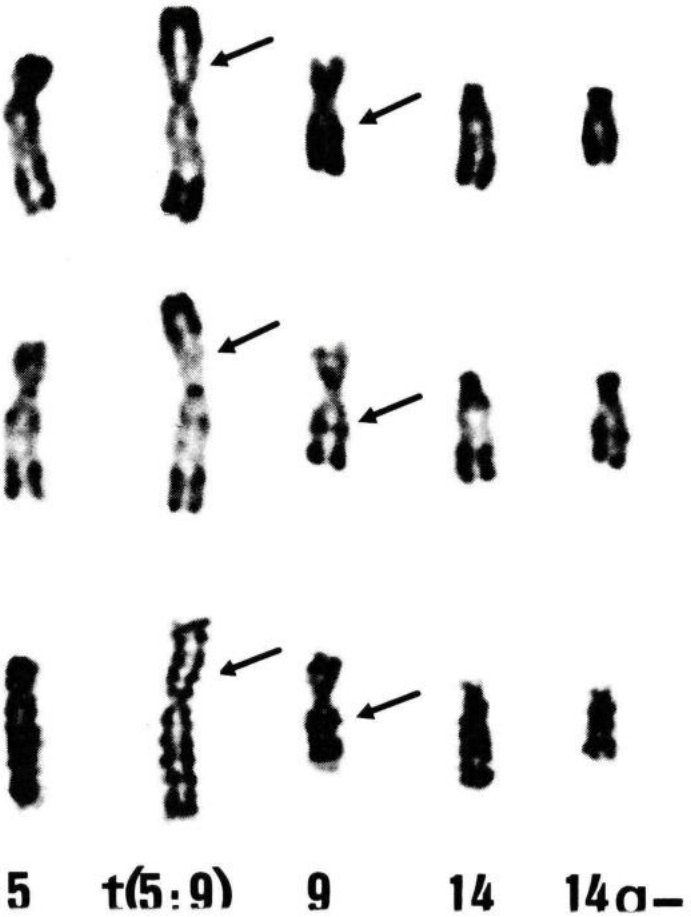


Figure 1 (b) Partial karyotypes showing balanced t(9;14)(p21;q12) and del(14)(q22q24) (RHG and GTG bands).

Figure 2 Partial karyotype of patient 2 showing der(5)t(5;9)(p14;q21) associated with 14q deletion (RHG and GTG bands).



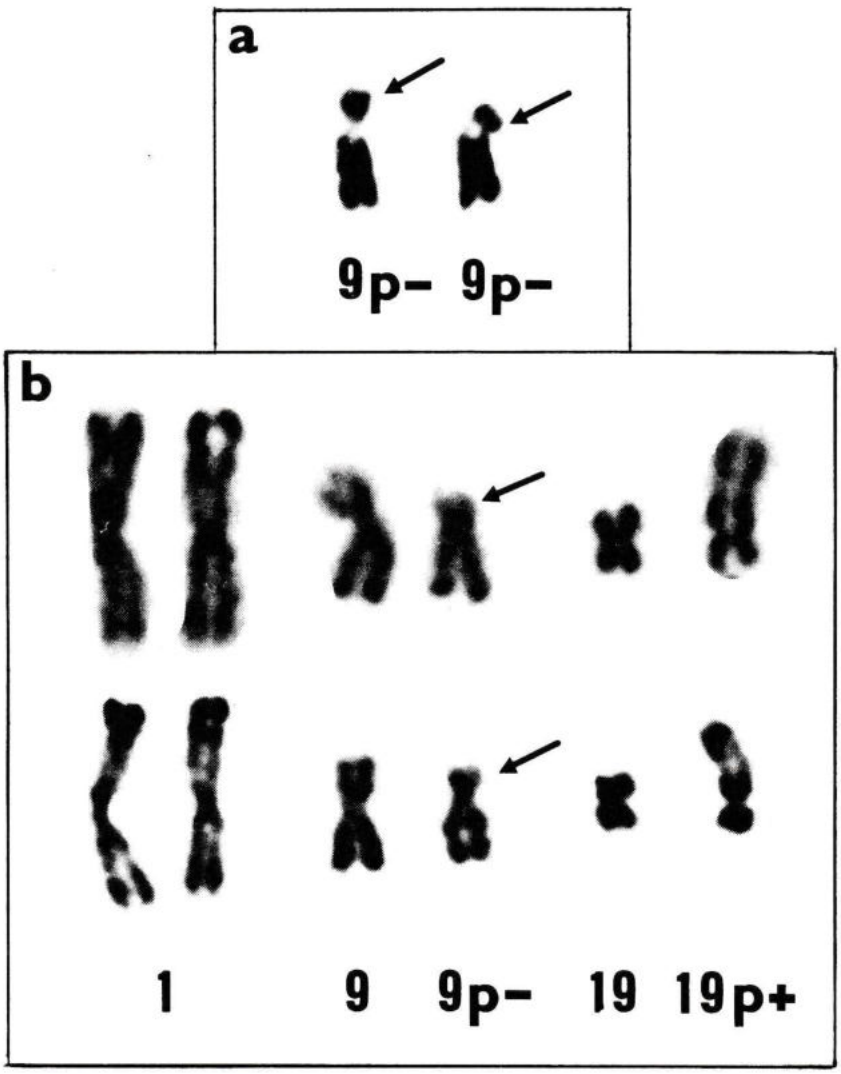


Figure 3 (a) R-banded partial karyotype of patient 3: del(9)(p21) and del(9)(p13). (b) R-banded partial karyotype of patient 4: del(9)(p21) and der(19)t(1;19)(q21;p13).

balanced translocation in the other patient. These structural abnormalities have been described by different authors: single 9p deletion [1, 2, 7–9], loss of the whole chromosome [1–3], deletion by unbalanced translocation [2, 3, 8, 11], as in patient 2, and by balanced translocation [3, 8], as in patient 1. A 9p− has also been found in pre B-ALL [10] associated with t(1;19). Kowalczyk and Sandberg [1] first reported the association between 9p− or monosomy 9, lymphomatous ALL (i.e., splenomegaly, marked lymphadenopathy with or without mediastinal mass), high leukocyte count and T-cell or non-T non-B origin in children and adolescents (mean age 10.7 years). Chilcote et al. [2] confirmed their results. To our knowledge, 31 cases of ALL with chromosome anomalies involving 9p (including our four patients) have now been reported (Table 4). Although the three largest series [1–3] comprised children or adolescents only, several adult cases have also been reported [8, 9], and in our series, adults predominated. A slight male predominance was encountered in all reports. Lymphomatous features were found in 19 of 31 and leukocyte counts above 50×10^9/L were seen in 17 of 31 patients. Immunologically, out of 24 patients adequately studied, seven were T, 13 common and 4 null ALL (although in the latter cases, early T or pre-B ALL could not be ruled out because of the small number of markers analyzed).

Acute lymphocytic leukemia with 9p anomalies therefore appears to be more heterogeneous than first reported [1, 2, 12]. Discrepancy in patient age might be explained by different referral among institutions. Our 128 L-1 or L-2 ALL patients

Table 4 List of reported cases of all with 9p chromosome changes: clinical, hematologic and immunologic characteristics

Patient	Age/sex	Bulk disease	WBC ($\times 10^9$/L)	Morphology, FAB	Immunologic results				Karyotype abnormalities	Reference
					CALLA	Ia	B	T		
1	F	Bulk disease 6/7	>60,000	[a]	−	−	−	+	t(9p;21q+),14q+,+21	[1]
2	M			[a]	−	−	−	+	t(1;1)(q41;q25),+4del(6)(q21),−7,+9, del(9)(p13),−12,+16,+17,+21,+21,+m	[1]
3	M			[a]	−	−	−	+	del(5)(q15q31),del(9)(p21)	[1]
4	M			[a]	−	−	−	+	del(6)(q21),del(9)(p11)	[1]
5	M			[a]	−	−	−	−	del(9)(p21)	[1]
6	F			[a]	−	−	−	+	−9	[1]
7	F			[a]	−	−	−	−	−9,i(17q)	[1]
8	16/M	+	5	L-1			−	−	−9,−9,+2min	[2]
9	10/M	+	207	L-1			−	+	−8,−9,+der(9)t(8;9)(q12;p13),del(6)(q12?q21?)	[2]
10	18/F	+	24	[a]			NT	NT	del(7)(p15),del(9)(p2100 p2200)	[2]
11	4/M	+	37	L-1			−	+	del(9)(p22),del(20)(p12)	[2]
12	1/F	+	150	L-1			−		−20,+21,del(9)(p2100 p2200)/+21,del(9)	[2]
13	4/F	−	27	[a]	+	+	−	−	del(9)(p13)	[7]
14	15/F	+	13.9	[a]			−	−	t(9;18)(p24;q12)	[8]
15	55/M	−	130.4	[a]	+	+	−	−	del(9)(p22)	[8]
16	41/M	+	283.5	[a]	+	+	+	−	−9,+der(9)t(4;9)(9;22)(q11;p13;q34;q11)	[8]
17	41/F	−	12.4	[a]	+	+	+	−	del(9)(p21)	[8]

18	12/F	−	3	L-1–L-2			NT	−	del(9)(p21)	[9]	
19	15/M	+	232	L-2			−	−	del(6)(q21q23?),del(9)(p22),del(11)(q13), del(6),del(7),del(9),del(11)/−6,del(9), del(11),+i(6p)	[9]	
20	36/F	−	7.8	L-1			−	−	del(9)(p21),t(12;17)(p13;q12)	[9]	
21	14/F	−		[a]	+		−	−	−9,−13,18,+X,+2,+4,+5,+5,+6,+8,+8, +10,+10,+20,+21,+21,+22,+der(9) t(9;13)(p21;q13)	[3]	
22	7/M	−		[a]	+		−	−	−9,−12,+mar	[3]	
23	8/M	−		[a]	+		−	−	t(2;12)(p13;p12),t(9;10)(p22;q21)	[3]	
24	16/M	−	<50,000	[a]	+		−	−	−9,−12,+der(9;12)(p11;q11)	[3]	
25	7/M	−		[a]	+		−	−	−15,+X,+2,+4,+5,+8,+10,+11,+12,+14, +18,+19,+20,+21,+21,+del(6) (q21),der(9)t(9;?)(p13;?)	[3]	
26	4/M	−		[a]	+		−	−	−1,der(6),dic(6;?)(p25;?),−9,del(7)(q22), der(9)t(9;?)(p13;?)	[3]	
27	8/M	+		[a]	+		−	−	del(7)(p15),dic(9;12)(p11;p13)	[3]	
28	11/M	+	600	L-1	+	+	−	−	−9,der(9)t(9;14)(p21;q12),del(14) (q22q24)	case 1	Present report
29	37/M	+	52	L-1	−	−	−	−	−5,−9,+der(5)(5;9)(p14;q21),del(14) (q22q24)	case 2	
30	36/M	+	64.7	L-2	+	+	−	−	del(9)(p13),del(9)(p21)	case 3	
31	25/F	+	150	L-1–L-2	−	−	−	−	−19,del(9)(p21),der(19)t(1;19)(q21;p13)	case 4	

Abbreviation: NT, not tested.

[a]not evaluated

institutions seem to deal essentially with pediatric patients [2, 3]. Heterogeneity of clinical presentation and immunologic features might be related to the variability of karyotypes among reported cases. Out of 31 patients (Table 4), 9p− anomalies were isolated in only six cases, and associated with other clonal anomalies in the remaining patients including five del(6), four del(7), one del(11), two del(14), one del(5), and one del(20). Additionally, we found a 9p deletion in two of our ALL patients with a Ph chromosome [13], and this association has been reported in another case (patient 16, Table 4). The question of whether del(9p) represents a primary or secondary chromosome defect can therefore be raised. It must be noted, however, that the 9p21-22 region is also involved in other leukemias, particularly in t(9;11)(p21;q23) translocations (monocytic leukemias) [12, 14], and that a heritable fragile site exists in that region [15]. Finally, the gene encoding the enzyme methylthioadenosine phosphorylase (MTAP), which is involved in purine metabolism in proliferating lymphocytes, has been located on the short arm of #9 [16]. This enzyme was absent in blasts of ALL patients with 9p− deletion [17]. Although MTAP deficiency has also been encountered in cases of ALL without 9p anomalies [18], it may render the malignant clone sensitive to agents that inhibit de novo purine synthesis [17].

The 9p− abnormalities appear relatively frequently in childhood and adult ALL. Although ALL with 9p− defects may not represent a homogeneous subgroup of ALL, they are still associated, in the majority of patients with poor prognostic features, such as older age for children, bulk disease, and T-cell or null origin.

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