Relation Among Occupational Exposure to Potential Mutagenic/Carcinogenic Agents, Clinical Findings, and Bone Marrow Chromosomes in Acute Nonlymphocytic Leukemia

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The chromosome banding pattern of bone marrow cells and clinical findings, including cytologic diagnosis, response to therapy, and survival time, were compared in two groups of adult patients with acute nonlymphocytic leukemia (ANLL): 23 patients occupationally exposed to chemical solvents, insecticides, and petrol products and 33 patients with no history of occupational exposure to potential mutagenic/carcinogenic agents. As regards clinical findings, cases classified as AML were more common in the exposed group, whereas the monocytic varieties of ANLL were more common in the nonexposed group; neither the complete remission rate nor the median survival differed significantly. In both groups patients with only abnormal metaphases had poorer prognoses than those with normal bone marrow metaphases only. The detailed karyotypic findings showed striking differences between the two groups: (1) in the nonexposed group only 24.2% had chromosome aberrations, whereas 82.6% of the exposed patients had aberrations; (2) in the exposed group 84.2% of the patients with aberrations had at least one of four particular changes—monosomy 5 or 7 or trisomy 8 or 21, but in the nonexposed group none of the patients had monosomy 5 or trisomy 8, and only one patient had monosomy 7 and one had trisomy 21. None of the remaining aberrations seen in the nonexposed group were found in any of the exposed individuals.

RECENT STUDIES on patients with acute nonlymphocytic leukemia (ANLL) whose bone marrow cells were analyzed with chromosome banding techniques have yielded the following main conclusions: (1) About 50% of the patients have no apparent chromosomal aberrations.[1-5] (2) When present, the aberrations are nonrandom, with a preferential engagement of chromosomes 5, 7, 8, and 21. (3) The presence of chromosome abnormality at diagnosis has prognostic implications—patients with exclusively normal bone marrow chromosomes have a significantly better prognosis than those with abnormal bone marrow metaphases.[5-9]

A clarification of the biologic mechanisms underlying these results is of the utmost importance for an understanding of the role played by chromosome abnormalities in the causation and/or evolution of acute leukemia. During the last five years evidence has accumulated from work with experimental tumors indicating that the etiologic agent is of prime importance in determining the karyotypic pattern of malignant cells.[10-14] As far as human tumors are con-

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cerned, however, this interpretation is still only an attractive but unproven hypothesis. Detailed analysis of the karyotypic patterns of malignant cells in patients occupationally exposed to mutagenic/carcinogenic agents may, however, offer an opportunity to test the possible relationship between etiology and chromosome aberration. In the current study chromosome findings in patients with ANLL were correlated with occupational exposure to potentially leukemogenic chemical agents.

MATERIALS AND METHODS

Since 1972 chromosome analysis of bone marrow cells has been attempted, often repeatedly, in all patients with acute leukemia hospitalized in or attending our hospital. Between July 1, 1972 and October 31, 1977, analyses of bone marrow chromosomes with the trypsin-Giemsa banding technique were successful in 93 patients with acute leukemia. These patients comprised approximately 90% of the total and should therefore represent an unselected group.

The case records of all patients were reviewed and their occupations categorized by one of us (P.G.N.) without any knowledge of the chromosomal findings. In the records of 37 patients ambiguous or no data were given regarding the profession. This report is based on the 56 adult patients with ANLL whose case records contained sufficient information on present or previous occupations to make it possible to classify each of them as either professionally not exposed or clearly exposed to mutagenic/carcinogenic chemical agents. None of the patients were interviewed about social and private habits including hobbies, smoking, alcohol and coffee consumption, use of cosmetics or hair dyes, etc. Patients previously treated for other malignancies as well as patients with a myeloproliferative condition preceding the acute leukemic phase were excluded.

The group of patients regarded as nonexposed included housewives, students, and white-collar workers. The exposed individuals were divided into three groups according to exposure to (1) chemical solvents (printing and glue workers, painters, dyers, rubber-factory workers), (2) insecticides (spray workers, gardeners), and (3) petrol products or their combustion residues (service station attendants, bus and truck drivers, motor vehicle mechanics, machinists).

Giemsa-stained preparations of the original bone marrow aspirates and peripheral blood were available for all cases; they were reexamined and reclassified by one of us (L.B.) without any knowledge of the chromosome or clinical findings. All cases were cytologically classified using the criteria established by the French-American-British (FAB) cooperative group.[15] The following designations and abbreviations were used for the six main myeloid leukemia types (M1 M6) of the FAB classification: acute myeloid leukemia (AML) for M1 and M2, acute promyelocytic leukemia (APL) for M3, acute myelomonocytic leukemia (AMMoL) for M4, acute monocytic leukemia (AMoL) for M5, and erythroleukemia (EL) for M6.

The clinical courses of the 56 patients were carefully reviewed. Response to treatment—no response (NR), partial remission (PR), and complete remission (CR)—and survival time calculated from the day of diagnosis—were established for each patient. Different chemotherapy schedules were used, and 7 patients, mainly elderly patients, did not receive chemotherapy (NT).

The chromosomes were studied in direct bone marrow preparations at the time of diagnosis. At the time of specimen withdrawal no patient had received chemotherapy or radiation therapy. The trypsin-Giemsa banding technique used has been described previously.[1] Karyotype analysis with G banding was made by photography, each karyotype in addition being checked directly in the microscope. The chromosomes were classified according to the criteria recommended by the Paris Conference (1971).[16] An abnormal clone was defined as at least two cells with the same extra chromosome or structural rearrangement or three cells with the same missing chromosome.

RESULTS

The group of 56 patients consisted of 29 females and 27 males with an age range of 15–83 yr (median 57); 29 patients (51.8%) had a normal bone marrow karyotype, whereas 27 patients (48.2%) had clonal chromosomal changes—in 15 of these patients all bone marrow cells showed an abnormal karyotype,

while 12 patients had both abnormal cells and normal diploid cells. Age, sex, cytologic diagnosis, bone marrow karyotype, response to treatment, and survival time data are summarized in Tables 1 and 2. The karyotypic findings in 4 patients with aberrations (cases 26, 31, 38, and 47) have been described previously.[1]

Thirty-three patients (cases 1–33, Table 1) had no apparent previous occupational exposure to mutagenic/carcinogenic agents. This group consisted of 21 females and 12 males with an age range of 15–83 yr (median 62). Twenty-three patients (cases 34–56, Table 2), 8 females and 15 males with an age range of 20–74 yr (median 53) had a history of occupational exposure to solvents (cases 34–46), insecticides (cases 47–49), and petrol products (cases 50–56). Cytologic, clinical, and chromosomal characteristics are presented below and comparisons made between the two groups, nonexposed versus exposed.

Cytologic correlations. The cytologic diagnoses (FAB classification) are given in Table 3. A difference between the exposed and the nonexposed group

Table 1. Clinical and Chromosomal Characteristics of 33 Nonexposed Patients With ANLL

Case No.	Age (yr)/sex	Diagnosis	Karyotype	Response to Treatment	Survival (mo)
1	26/F	AMoL	46,XX	CR	13
2	69/F	AMMoL	46,XX	NR	11+
3	40/F	AML	46,XX	CR	16
4	65/F	AMMoL	46,XX	CR	—
5	35/F	AML	46,XX	NR	9
6	74/F	AML	46,XX	NR	5
7	20/F	AMMoL	46,XX	CR	18
8	48/F	AML	46,XX	CR	24
9	28/F	AML	46,XX	NR	1
10	71/F	AML	46,XX	NT	5+
11	54/F	AML	46,XX	CR	8
12	26/F	AMMoL	46,XX	NT	0+
13	80/F	AMMoL	46,XX	NR	5
14	64/F	AML	46,XX	CR	13
15	15/M	AMMoL	46,XY	NR	2
16	73/M	AML	46,XY	NR	4
17	43/M	AML	46,XY	CR	5+
18	78/M	AMMoL	46,XY	NR	2
19	65/M	AML	46,XY	NR	14
20	61/M	AMoL	46,XY	NR	1
21	64/M	AMMoL	46,XY	NT	1+
22	79/M	AMoL	46,XY	NT	4+
23	23/M	AMMoL	46,XY	NR	5
24	57/M	EL	46,XY	NR	5
25	77/M	AMMoL	46,XY	NR	18
26	51/F	AML	45,XX,−7/46,XX	NR	5
27	64/F	AML	47,XX,+21/46,XX	PR	16+
28	83/F	AML	47,XX,+del(9)(q13)/46,XX	NR	2
29	49/F	AML	46,X,del(X)(q21),t(5;21)(q13;q22)	NR	5
30	68/F	AML	46,XX,t(16;16)(p13;q22)	NR	1
31	77/F	AMMoL	46,XX,iso(17q)	NR	11
32	15/F	AML	46,XX,t(8;16)(p11;p13)	NR	1
33	62/M	APL	47,XY,del(12)(p11),del(20)(q11),+9	NR	2+

Table 2. Clinical and Chromosomal Characteristics of 23 Exposed Patients With ANLL

Exposure	Case No.	Age (yr)/ Sex	Diagnosis	Karyotype	Response to Treatment	Survival (mo)
Solvents	34	63/F	AML	44,XX,+8,−12,−13,−14,t(2;5)(q12;q35)/46,XX	NR	1
	35	40/F	AML	45,X,−X,t(8;21)(q21;q22)/46,XX	NR	4
	36	44/F	AML	45,XX,−7/46,XX	CR	2
	37	26/M	AML	46,XY,t(9;22)(q21;q22)/46,XY	CR	10
	38	55/M	AMMoL	46,XY,+8,−17/47,XY,+8/46,XY	NR	3
	39	74/F	AML	48,XX,+3,+8/46,XX	NR	1
	40	65/M	APL	45,XY,t(3;12)(p14;q24),t(13;18)(q11;p11)/ 51,XY,t(3;12),t(13;18),+1,+6,+16,+19,+21, +22	NR	9+
	41	20/F	AML	46,XX,del(5)(q14)	CR	7
	42	53/M	AML	46,XY,del(7)(q31),del(11)(q14),del(12)(p12)	CR	12
	43	60/F	AML	47,X,−X,+del(1)(p11),del(5)(q13),t(5;12) (q21;q24),t(11;12)(q25;q13),t(13;14)(q11; p11),+16,+21	CR	3+
	44	52/F	AML	47,XX,+8	CR	4+
	45	67/M	AML	47,XY,+8	NT	1
	46	74/F	AML	48,XX,t(1;3)(q44;p14),del(3)(q21;p14),−5, +10,+11,+21	NT	3+
Insecticides	47	57/M	AMMoL	47,XY,+21/46,XY	NR	2
	48	66/M	AML	45,XY,−7	NT	2
	49	70/M	AMoL	47,XY,del(7)(q22),+del(8)(q12)	NR	1
Petroleum products	50	23/M	AML	46,XY	NR	7
	51	36/M	AML	46,XY	CR	9
	52	41/M	AML	46,XY	CR	18
	53	46/M	EL	46,XY	CR	16
	54	29/M	AMMoL	45,X,−Y/46,XY	CR	6
	55	32/M	AML	45,XY,+2,−5,−7/46,XY	PR	5
	56	57/M	AML	44,XY,−5,t(5;12)(q12;q24),iso(18q),−19	NR	1

was noted. The monocytic varieties of ANLL (M4, M5) constituted only 17.4% of the exposed patients in contrast to 42.4% of the nonexposed patients, whereas more patients classified as having AML were found in the exposed than in the nonexposed group (73.9% versus 51.5%). The frequencies of APL and EL were similar in both groups.

Chromosomal–clinical correlations. In Table 4 the karyotypic findings have been grouped according to the presence or absence of cells with chromosome aberrations: NN, normal metaphases only; AN, normal and abnormal metaphases; AA, abnormal metaphases only. There is a striking difference between the exposed and the nonexposed groups. In the former, 19 of 23 patients (82.6%) had abnormal bone marrow metaphases, whereas in the nonexposed

Table 3. Cytologic Correlations

Group	Cytologic Diagnosis (%)			
	AML (M1, M2)	AMoL + AMMoL (M4, M5)	APL (M3)	EL (M6)
Nonexposed	51.5	42.4	3.0	3.0
Exposed	73.9	17.4	4.3	4.3
Total	60.7	32.1	3.6	3.6

Table 4. Presence of Chromosomal Abnormality (NN, AN, AA) and Survival

Group	No. of Patients			Median Survival (mo)		
	NN	AN	AA	NN	AN	AA
Nonexposed	25 (75.8%)	3 (9.1%)	5 (15.2%)	7.0	3.5	3.0
Exposed	4 (17.4%)	9 (39.1%)	10 (43.5%)	12.5	3.0	1.5
Total	29 (51.8%)	12 (21.4%)	15 (26.8%)	8.5	3.0	1.5

group the corresponding figure was only 8 of 33 (24.2%). The difference was significant ($p < 0.01$). The predominance of abnormal karyotypes in the exposed compared to the nonexposed group was similar in AML (14/17 versus 6/17) and in the monocytic varieties of ANLL (4/4 versus 1/14).

The median survival times are also presented in Table 4. Patients alive at this writing were excluded when calculating median survival. There was no difference in survival time between the nonexposed and the exposed patients, but the same trend was obvious in both groups: patients who had only abnormal metaphases (AA) had a poorer prognosis than those with only normal metaphases (NN).

Karyotypic correlations. In the total group 27 patients had an abnormal karyotype. Loss or deletion of the long arm of chromosome 5 was present in five cases, loss or deletion of the long arm of chromosome 7 in six cases, trisomy 8 in six cases, and trisomy 21 in five cases. Altogether, at least one of these four aberrations was present in 18 of the 27 patients with chromosome abnormalities (66.7%). The incidence of major specific karyotypic changes among exposed and nonexposed patients is summarized in Table 5. In the exposed group monosomy 5 or deletion of the long arm of chromosome 5 was found in five patients (three exposed to solvents, two to petrol products), monosomy 7 or deletion of the long arm of chromosome 7 in five patients (two exposed to solvents, two to insecticides, one to petrol products), trisomy 8 in 6 patients (five exposed to solvents, one to insecticides), and trisomy 21 in four patients (three exposed to solvents, one to insecticides). One of these four

Table 5. Incidence of Specific Chromosome Aberrations in 27 Patients With ANLL

Karyotype	Number of Clones in:	
	Exposed Patients (n = 19)	Nonexposed Patients (n = 8)
−5/5q−	5	—
−7/7q−	5	1
+8	6	—
+21	4	1
−X,t(8;21)	1	—
t(9;22)	1	—
−Y	1	—
+9	—	2
i(17q)	—	1
t(5;21)	—	1
t(8;16)	—	1
t(16;16)	—	1

changes was present in 16 of the 19 patients (84.2%). In the nonexposed group none of the patients showed a loss or a deletion of chromosome 5 or trisomy 8 and only one patient showed monosomy 7 and one trisomy 21. None of the aberrations seen in the remaining nonexposed patients were seen in the exposed group.

DISCUSSION

The present series of patients with ANLL was selected on the basis of available information regarding past and present occupational history. Such information is more likely to be absent in case records of older individuals, and the slightly lower median age of our patients (57 yr) as compared to a median age of 60–64 yr in adult patients with ANLL in our country may be due to such a selection. On the other hand, all clinical and cytogenetic parameters were in accordance with an unselected group of patients with ANLL: the sex ratio was equal, the CR rate of treated patients was 36%, the median survival time from diagnosis was 5 mo, about 50% of the patients had chromosome aberrations at diagnosis, and these aberrations were clearly nonrandom with a preferential engagement of chromosomes 5, 7, 8, and 21. These findings agree perfectly with previously published data[1-4] and with results recently obtained at the First International Workshop on Chromosomes in Leukemia, where 279 unselected cases of ANLL, collected from seven laboratories, were reviewed.[5]

In the present group 23 of the 56 patients had a history of exposure to chemical solvents, insecticides, and petroleum products or their combustion residues. It must be emphasized that occupational titles and other data obtained from case histories give very crude information on occupational hazards, and the recorded frequency of exposed individuals probably grossly underestimates the real frequency of occupational exposure to potentially mutagenic/carcinogenic agents. Furthermore, since the occupations recorded included a number of different, sometimes very ill-defined professions, it is impossible to estimate the frequency of such professions in the general population. It is therefore not known whether or not these professions were unduly common in our patients with ANLL. There is, however, information available as far as exposure to petroleum products is concerned. Using the same criteria for exposure as in the present study, we recently showed[17] that in the general population only about 10% of males of ages 20–65 yr are occupationally exposed to petroleum products, whereas the frequency of such occupations in males with ANLL in the same age group was 36%. In the present series, there were 19 males of ages 20–65 yr, 7 of whom were exposed to petroleum products, i.e., the same frequency as found in our previous study. It remains to be clarified whether or not occupational exposure to insecticides or chemical solvents is also increased in leukemic patients.

The various types of ANLL were not equally represented in the nonexposed and the exposed patients. The most conspicuous discrepancy was the different incidence of the monocytic varieties of ANLL in the two groups. In ANLL cases classified according to the FAB criteria as AMoL and AMMoL have been found to constitute 28%–31% of the patients,[5,18] which is in good agreement with the proportion (32%) found in our total group. However, the monocytic

varieties of ANLL were strikingly uncommon (17%) in our exposed group, whereas there was a heavy predominance of patients with the other types of ANLL, mainly AML. It is interesting to note that in ANLL patients chronically exposed to benzene a similar low frequency of the monocytic varieties may occur. Thus among 27 such patients reported by Aksoy[19] only three cases of AMMoL and AMoL were found (11%). It is therefore possible that the monocytic types of ANLL are relatively uncommon sequelae of exposure to chemical leukemogenic agents.

In the present study there were striking differences between the chromosomal findings in the nonexposed versus the exposed group: (1) In the nonexposed group only 24.2% of patients had chromosomal aberrations in their bone marrow cells, whereas 82.6% of the exposed patients had chromosome aberrations. (2) In the exposed group 16 of 19 patients with aberrations (84.2%) showed one or more of four particular changes: monosomy or deletion of chromosome 5, monosomy or deletion of chromosome 7, trisomy 8, or trisomy 21, but in the nonexposed group 8 patients had chromosome aberrations; none of these patients had monosomy 5 or trisomy 8, one patient had monosomy 7, and one had trisomy 21. Of the remaining six patients in the nonexposed group two had trisomy 9, one had an isochromosome 17, and three each had a different balanced translocation: t(5; 21), t(8; 16), and t(16; 16). None of these aberrations were seen in any of the exposed individuals. Similarly, each of the three exposed patients without monosomy 5 or 7 or trisomy 8 or 21 had a different karyotype: −Y, t(8; 21), and t(9; 22). None of these aberrations were seen in the nonexposed patients. These differences between the exposed and the nonexposed groups strongly indicate that the karyotypic patterns of the leukemic cells were, in fact, influenced by the exposure.

The high frequency of chromosomal aberrations in the leukemic cells of patients exposed to potential leukemogenic chemical agents may be an interesting parallel to results obtained in experimental tumors. It has been shown that these may start with a normal karyotype that eventually changes to an abnormal one by a predetermined stepwise karyotypic evolution,[20] and the rate of this chromosomal progression may depend on the inducing agent. In Rous virus induced sarcomas of the rat about 50% of early tumor stages have a normal diploid karyotype,[21] whereas histologically identical sarcomas in the same species but induced with chemical agents—dimethylbenzanthracene, benzpyrene, and methylcholanthrene—are characterized by a high (sometimes almost 100%) incidence of abnormal karyotypes.[12,22] It is possible that also in human ANLL inducing agent(s) may influence the rate of the chromosomal evolution from a normal to an abnormal karyotype.

The presence or absence of chromosomal abnormality in bone marrow cells has prognostic implications. Sakurai and Sandberg[6,7] first reported that patients without any normal metaphases in their bone marrow had a significantly shorter survival than those with at least one normal diploid bone marrow metaphase. This observation has recently been confirmed in patients studied with banding technique[5,8,9] and finds further support in the present study; the median survival of patients with exclusively normal chromosomes (NN) was 8.5 mo, whereas that of patients with abnormal chromosomes (AA) was only 1.5 mo.

There was no significant difference between the exposed and the nonexposed patients; both groups showed the same trend.

Nonrandom patterns of chromosome aberrations have been shown in all experimental and human neoplasms studied with banding techniques in a number sufficient to permit conclusions. In both experimental and human tumors the aberrations tend to cluster to a few chromosomes,[23-25] possibly indicating that genes of prime importance in malignant development are not scattered evenly over all chromosomes but accumulate on specific ones. Furthermore, results from experimental studies strongly indicate that the etiologic agent is of prime importance in determining the karyotypic pattern,[10-14] certain chromosomal regions possibly being specifically vulnerable to the chromosome-damaging action of different carcinogens.[26,27] The nonrandom engagement of a few chromosomes would then be the result of a preferential interaction between the inducing agent and those chromosomes containing genetic material of importance for tumor development. The nonrandom engagement of chromosomes 5, 7, 8, and 21 in patients exposed to different chemical solvents, insecticides, and petrol products reported here may support this hypothesis. The clear differences in karyotypic aberrations between nonexposed and exposed patients also support the general conclusion that etiologic factors do influence the karyotypic pattern of malignant cells not only in animals but also in man.

The present data on exposure to potential mutagenic/carcinogenic agents were obtained from case records; the information on environmental hazards is therefore incomplete. It should also be emphasized that a considerable number of patients had to be excluded from the study because the records were insufficient regarding their profession; this omission may be a source of bias. Nevertheless, the results suggest that correlations might exist between leukemogenic agents, cytologic type of leukemia, and chromosome progression of the leukemic cells. We recently found that close questioning of ANLL patients yielded valuable information on environmental risk factors.[28] Future thorough environmental investigations combined with a standardized cytologic classification and detailed chromosome analyses may therefore be important in defining etiologic agents in ANLL.

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