Chromosome Analysis of 63 Cases of Secondary Nonlymphoid Blood Disorders: A Cooperative Study

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ABSTRACT: A cooperative study of secondary nonlymphoid blood disorders [dysmyelopoietic syndrome and acute nonlymphoblastic leukemia (ANLL)] was carried out on **63** patients, 8 after professional exposure to carcinogenic agents and 55 following exposure to therapeutical hazards. Clonal chromosome abnormalities were observed in 56 cases (88.9%). The most common abnormalities were hypodiploidy and structural defects. The chromosomes most often involved were #7, #5, and #17. Monosomy 7 was seen more often following malignant lymphoma than after cancer, whereas monosomy 17 seemed more common in patients formerly exposed to professional hazards. Cytogenetic "variation" is often accompanied by cytologic "variation," which could explain the high proportion of ANLL cases that are difficult to classify into the FAB system. A correlation was found between complete monosomy 7 and the presence of micromegakaryocytes and/or macroplatelets.

INTRODUCTION

Acute nonlymphoblastic leukemia, secondary to exposure to carcinogenic agents in either a professional or therapeutic context, is becoming more and more common. Recent cytogenetic studies have shown that the chromosome abnormalities present in secondary acute nonlymphoblastic leukemia (ANLL), on the whole, are different from those in what is known as primary ANLL. The abnormalities are more frequent, as well as more complex; the structural abnormalities often are observed; and the number of chromosomes is frequently hypodiploid. Furthermore, certain chromosomes are more specifically involved, namely, chromosomes #5, #7, and #17 [1]. Since secondary ANLL and dysmyelopoietic syndromes (DMS) are relatively uncommon compared with the primary forms, a cooperative study was undertaken in order to analyze the chromosome abnormalities present, with a view to determine the types of abnormalities and to search for possible correlations with the cytologic aspect of these forms of leukemia.

MATERIALS AND METHODS

The cytogenetic study involved **63** cases (**32** men and **31** women; **48** ANLL and **15** DMS) diagnosed between **1975** and **1982,** who had not undergone treatment for the blood disorder at the time of the first chromosome examination (excluding case 2).

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Received August 1, 1983; accepted September 28, 1983.

Cancer Genetics and Cytogenetics **12,** 95–104 (1984)
0165-4608/84/$03.00

Table 1 Clinical and hematologic data on **63** patients

Case	Age at diagnosis of AL/Sex	Primary disease or occupational exposure	Therapy	Interval between treatment and secondary disease (yr)	Diagnosis[a]	Therapy of AL or MDS	Status[b]
1	55/M	Hodgkin's disease	R + C	4	UMDS	N	D (8m)
2	58/F	Hodgkin's disease	R	6	M1	Y	D (2m)
3	30/M	Hodgkin's disease	R + C	7	UAL	Y	D (14m)
4	69M	Hodgkin's disease	R + C	10	M2	Y	D (16m)
5	69/M	Hodgkin's disease	R + C	5	UAL	N	D (1m)
6	69/M	Hodgkin's disease	R + C	6	M4	Y	D (10m)
7	50/M	Hodgkin's disease	R + C	6	UAL	Y	A (7m)
8	34/F	Hodgkin's disease	R + C	9	RAEB-T	Y	D (2m)
9	23/M	Hodgkin's disease	R + C	4	UAL	Y	D (10m)
10	20/F	Hodgkin's disease	R + C	4	UAL	Y	D (4m)
11	66/F	Hodgkin's disease	R + C	6	M1	N	D (2m)
12	48/M	Hodgkin's disease	R	6	UAL	Y	D (8m)
13	54/M	Malignant lymphoma	R + C	6	M2	Y	D (3m)
14	89/F	Malignant lymphoma	R + C	15	UAL	N	D (1m)
15	26/F	Malignant lymphoma	C	3	CMML	Y	D (2m)
16	65/M	Malignant lymphoma	R + C	6	M2	N	D (1m)
17	78/F	Malignant lymphoma	C	8	RAEB	N	D (1m)
18	49/M	Malignant lymphoma	R + C	4	UMDS	Y	D (1m)
19	70/M	Multiple myeloma	C	3	UAL	Y	D (3m)
20	84/F	Multiple myeloma	C	4	UMDS	N	D (9m)
21	60/F	Multiple myeloma	C	5	M2	N	D (8m)
22	65/M	Multiple myeloma	C	6	M4	Y	D (2m)
23	60/F	Multiple myeloma	C	6	M2	N	D (5m)
24	42/M	Multiple myeloma	R + C	13	M4	Y	ND
25	58/M	Multiple myeloma	C	ND	M4	Y	ND
26	59/F	Macroglobulinemia	C	6	UMDS	N	D (5m)
27	56/F	Breast carcinoma	R + C	3	M6	N	D (2m)
28	80/F	Breast carcinoma	R	9	RA-S	N	A (6m)
29	62/F	Breast carcinoma	R + C	5	M2	N	D (1m)
30	73/F	Breast carcinoma	R + C	4	M6	Y	D (2m)
31	68/F	Breast carcinoma	R + C	8	M2	N	D (2m)
32	78/F	Breast carcinoma	R	2	M1	Y	D (1m)
33	69/F	Breast carcinoma	C	3	RAEB	N	D (1m)
34	84/F	Breast carcinoma	R	24	M2	Y	D (1m)
35	67/F	Breast carcinoma	R + C	4	M5	Y	D (5m)
36	57iF	Ovarian carcinoma	C	6	UMDS	N	A (3m)
37	77/F	Ovarian carcinoma	C	4	M4	Y	D (2m)
38	72/F	Ovarian carcinoma	R + C	5	M1	N	D (1m)
39	60/M	Renal adenocarcinoma	R	7	M5	Y	A (5m)
40	71/M	Epiglottis ca-cinorna	R	4	M1	Y	A (6m)
41	60M	Renal adenocircinoma	C	7	CMML	N	A (8m)
42	13/M	Glioma	R	13	M4	Y	D (9m)
43	54/M	Renal adenocarcinoma	C	3	M4	Y	D (1m)
44	69/F	Colonic carcinoma	C	3	M4	Y	D (1m)
45	43/M	Testicular seminoma	R	6	UAL	Y	D (9m)
46	73/F	Cervical carcinoma	R	8	M3	Y	D (1m)
47	33/F	Lung carcinoma	C	2	M5	Y	D (1m)
48	55/M	Renal adenocarcinoma	R + C	6	RAEB-T	N	D (6m)
49	39/M	Astrocytoma	R + C	3	UAL	N	D (7m)
50	68/F	Endometrial carcinoma	R + C	ND	RAEB	N	ND
51	38/M	Colonic carcinoma	C	5	UAL	Y	D (6m)
52	13/M	ALL	R + C	8	M4	Y	D (16m)

Table 1 (continued)

Case	Age at diagnosis of AL/Sex	Primary disease or occupational exposure	Therapy	Interval between treatment and secondary disease (yr)	Diagnosis[a]	Therapy of AL or MDS	Status[b]
53	49/M	Rheumatoid arthritis	C	8	UMDS	N	D (3m)
54	16/F	Glomerulonephritis	C	8	M2	Y	D (13m)
55	55/M	Multiple sclerosis	C	4	M4	Y	D (2m)
56	37/M	Benzene exposure	—	—	M1	Y	A (2m)
57	57/M	Hydrocarbure exposure	—	—	UAL	N	A (17m)
58	77/M	General irradiation	—	—	UMDS	N	A (1m)
59	78/F	General irradiation	—	—	M2	Y	D (1m)
60	42/M	Solvent use	—	—	UMDS	Y	D (1m)
61	40/M	Benzene exposure	—	—	M2	Y	D (1m)
62	28/F	General irradiation	—	—	M2	Y	D (7m)
63	48/M	General irradiation	—	—	UAL	Y	D (10m)

[a] M1, M2, M3, M4, M5. M6 categories of ANLL according to the FAB nomenclature; RAEB, refractory- anemia with excess of blasts: RAEB-T, RAEB in transformation; RA-S. refractory anemia with ring sideroblasts; CMML. chronic myelomonocytic leukemia; UMDS. unclassifiable MDS; UAL, unclassifiable AL.

[b] D, died; A. alive; m, months

The distribution was as follows: 8 patients had been professionally exposed to carcinogens, 3 patients had been treated with immunodepressors, and 52 patients previously had been treated for malignancy (Tables 1 and 2). Of the latter group, 10 patients had undergone localized radiotherapy exclusively. The time elapsed between initiation of treatment and date of diagnosis of the blood disorder varied from 2 to 24 years, with a median value of 5 years.

The chromosomes were studied using bone marrow (examined "directly" or cultured for 24, 48, or 72 hr), and/or unstimulated blood cultures (24, 48, and/or 72 hr) obtained at time of diagnosis of the secondary blood disorder and, in some cases, during the course of the illness.

GTG-, RHG-, RHA-, QFQ-, and occasionally CBG-banding techniques were used. Only those cases examined by banding techniques were included in this study.

All the files were reviewed by the members of the study group with a view to obtaining consistency in the interpretation of the results. ISCN nomenclature [2] was used.

The complexity of the chromosome abnormalities observed led us to define karyotype "variation" as a modification of the karyotype of a given clonal abnormality: for example, in different cells of a given patient, it is defined as the presence of excess chromosomes and/or rearrangement, in addition to one or several constant clonal abnormalities.

Isolated variations (a single abnormal cell) and artifact-induced variations were not taken into consideration. The cells were classified into AA, NN, and AN groups [3].

The cytologic study was carried out by the members of the Groupe Français de Morphologie Hematologique (GFMH).

We attempted to classify the cells according to FAB recommendations [4, 5] by two independent readings (G. F., P. F.). Furthermore, in examining the smears, special attention was paid to morphologic details that were not necessarily relevant in the FAB classification, among which were noted various megakaryocyte abnormalities (micromegakaryocytes, megakaryocytes with nonfragmented nucleus), the presence of circulating macroplatelets, and the different categories of blasts.

Table 2 Primary disease and type of treatment given

Primary disease	Local irradiation	Chemotherapy	Radiotherapy plus chemotherapy	Total number of cases
Hodgkin's disease	2"	2	10	12
Malignant lymphoma		6	4	6
Multiple myeloma		1	1	7
Waldenstrom's disease				1
Solid tumors				
Astrocytoma			1	1
Colon		2		2
Epiglottis	1			1
Glioma	1			1
Ovary		2	1	3
Lung		1		1
Kidney	1	2	1	4
Breast	3	1	5	9
Testis	1			1
Uterus	1		1	2
Acute lymphoblastic leukemia			1	1
Glomerulonephritis		1		1
Rheumatoid polyarthritis		1		1
Multiple sclerosis		1		1
Total	10	20	25	55

'Number of cases

Table 3 Karyotypes

Case no.	Variation		Karyotype
1	AN	–	45,XY, – 7,5q – /45 – 90,XY, – 7,5q – , + mar
2	AN	–	47,XX, + 11
3	AA	–	45,XY, – 7,12p –
4	NN	–	46,XX
5	AA	–	45,XY, – 5,t(1;6)/44,XY, – 5, – 7,t(1;6),der(12)/44,XY, – 4, – 5, – 7, – 12, + mar, + f
6	AA	–	45,XY, – 7/44,XY, – 7, – 21
7	NN	–	46,XY
8	AA	–	47,XX, + 8
9	AN	–	45,XY, – 7
10	AN	–	46,XX,5q –
11	AN	–	46,XX, – 7,t(1;3)
12	AN	–	45,XY, – 7, + min.
13	AA	+	44,XY, – 7, – 11,5q – ,9p + /44,XY, – 7, – 11,5q – ,9p + ,17p + ,19p + / 43,XY, – 7, – 11, – 18,5q – ,9p + ,17p + ,19p +
14	AA	+	46,X, – 5, – 6,11q + ,r(11), + mar1, + mar2
15	NN	–	46,XX
16	AA	+	45,XY, – 8, – 13, – 18,?5q – ,7q – ,20q + , + mar1, + mar2

Table 3 (continued)

Case no.		Variation	Karyotype
17	AA	−	45,XXq−,−7
18	AA	−	46,XY,6p+/45,XY,−7,6p+
19	AN	+	45,XY,−16,−19,+mar1/44,X,−7,−16,−19,+mar1, +mar2/44,XY,−16,−19,der(1),+mar1,+mar2
20	AA	+	45,XX,−6,−7,der(3),5q−,+mar,+f
21	AN	−	45,XX,−7
22	AA	+	44,XY,−13,−18,6p+/43,XY,−5,−13,−18
23	AA	+	46,XX,−7,+mar1/47,XX,−7,+mar1,+mar2
24	AN	−	46,XY,i(21q)
25	AA	−	46,XY,−13,+t(13q13q)
26	AN	−	46,XX,20q−/45,XX,−7,20q−
27	AA	+	43,XX,−4,−16,−17,−19,5q−,t(4;11),t(11;16),+mar,+dm,+min, +f/43,XX,id.,9q−/42,XX,id.,−1
28	AA	−	46,XX,5q−
29	AA	+	47,XX,+11
30	AA	+	45,XX,inv(2),−4,−5,−6,−7,−17,−21,7p+,+mar1,+mar2,+mar3
31	AA	+	45,XX,−5,tdic(5;17)/45,X,der(X),−5,tdic(5;17),7q−,9q−
32	NN	−	46,XX
33	AA	−	45,XX,−5/45,XX,−7,11q+
34	AA	+	42,XX,−3,−5,−9,−12,−14,−16,−17,−18,−19,+mar1,+mar2, +mar3,+mar6,+mar7/41,XX,−3,−5,−9,−12,−14,−16,−18,−19, +mar2,+mar3,+mar4,+mar5
35	AN	−	45,XX,−21,2p+,7q−,+mar/44,XX,−10,−21,2p+,7q−,+mar
36	AN	−	45,XX,−18,7q−
37	AA	+	46,XX,t(2;11)/46,XX,−12,+13,t(2;11),17p+/ 46,XX,+5,−6,−8,t(2;11),11p+
38	AN	+	46,XX,der(11)/47,XX,der(11),+r/48,XX,der(11),+r,+mar
39	AN	−	48,XY,+8,+5q−,19q+
40	NN	−	46,XY
41	AN	−	46,XY,7q−
42	AA	+	46,XY,t(11;19)
43	AA	−	46,XY,t(10;11)/46,XY,7q−,t(10;11)
44	AN	−	43,1q+,4p− (random losses)
45	AA	−	44,XY,−4,−5,−12,−17,−19,3p−,?5q−,11q−,+mar1,+mar2
46	AN	−	46,XX,t(15;17)
47	AN	−	45,XX,−22/47,XX,+21
48	AA	+	42−44,XY,−9,−20,5q−,+mar1/44−46,XY,−9,5q−,+mar1/ 44−47,XY,−9,5q−,+mar1,+mar2
49	NN	−	46,XY
50	AA	−	45,XX,−7
51	AA	+	45,XY,−5,−7,−15,+r
52	AA	−	46,XY,6p+
53	AN	−	43−73,XY,−5,t(7;17)/41−72,XY,−5,t(3;12),t(7;17)
54	AN	+	47,XX,+der(2)/49,XX,+10,+13,+mar
55	AA	−	45,XY,−7
56	AN	−	46,XY,−?8,−21,+mar1,+mar2/45,XY,−?8,−17,−21,+mar1,+mar2
57	NN	−	46,XY
58	AN	−	47,XY,+8,5q−
59	AA	+	43,XX,−6,−9,−17,der(2), + various inconsistent mar
60	AA	−	42,XY,−17,−18,−18,t(1;5),5q−,t(7;18),r(11),t(21;21)
61	AA	+	45,XY,−5,−8,−17,6q−,7q−,10p+,+r
62	AN	−	45,XX,−5,−8,−17,2p−,+r
63	AN	−	45,XY,−7

Table 4 Repartition of chromosome abnormality categories according to the nature of risk exposure

	NN	AN	AA	Total
Local irradiation	2"	4	4	10
Chemotherapy	1	9	10	20
Chemotherapy plus radiotherapy	3	7	15	25
Occupational exposure	1	4	3	8
Total	7	24	32	63

"No. of cases

The data obtained were coded and processed by microcomputer using programs developed by a member of the GFMH (F. S.).

Twelve of these cases (nos. 9, 10, 24, 25, and 3, 15, 16, 26, 30, 31, 36, 37) have been included in previous publications [6–10].

RESULTS

Clonal abnormalities were found in 56 cases (24 AN and 32 AA) and normal kayotypes in only 7 cases (2 of which had been previously treated with localized radiotherapy) (Table 3). The distribution into groups NN, AN, and AA according to treatment is given in Table 4. The median survival rate for the three groups, respectively, was 15, 6, and 3.5 mo (statistically nonsignificant).

Chromosome "variation" was observed in 21 cases (Table 5). The distribution of the abnormalities is given in Table 6. Hypodiploidy was the most frequently encountered numerical abnormality (31 cases), and structural abnormalities were found in 40 cases. The chromosomes most frequently absent or rearranged were chromosome #5 (26 cases, 12 of which exhibited 5q−), chromosome #7 (31 cases, 10 of which exhibited 7q−), and chromosome #17 (14 cases). Chromosomes #5 and #7 were involved together in 12 cases.

Defects of chromosome #17 most often consisted of a loss (9 cases) or structural rearrangement (5 cases). Chromosome #3 was abnormal in 3 cases and chromosome #12 in 6 cases (4 losses and 2 structural defects).

Marker chromosomes were found in 42.9% of the cases, and ring chromosomes occurred in 12.7% of the cases.

Double minute (dm) chromosomes were found in one case only and were associated with fragments. In another case, fragments were present, and a third case, a minute chromosome was associated with monosomy 7.

Table 5 Chromosomal "variation" according to the nature of risk

	Variation	Absence of variation	Total
Local irradiation	2"	6	8
Chemotherapy	7	12	19
Chemotherapy plus radiotherapy	8	14	22
Occupational exposure	4	3	7
Total	21	35	56

"Number of cases.

Table 6 Chromosome abnormalities according to the nature of risk exposure

	Local irradiation	Chemotherapy	Chemotherapy plus radiotherapy	Total	Occupational exposure	Total number of cases
Absence of abnormalities	2	1	3	6	1	7
Hypodiploidy		2	2	4		4
Hypodiploidy plus structural abnormalities	3	6	14	23	4	27
Pseudodiploidy	3	4	3	10		10
Hyperdiploidy	1		2	3	1	4
Hyperdiploidy plus structural abnormality	1		1	2	1	3
Trisomy #8	1		2	3	1	4
5q−	3	1	6	10	2	12
Monosomy #5	1	4	4	9		9
7q−		3	4	7	3	10
Monosomy #7	1	9	10	20	1	21
Abnormalities of #5 and #7		4	6	10	2	12
Abnormalities of #17	3	2	4	9	5	14
11q Abnormalities	2	2	2	6		6
Ring chromosomes		1	3	4	4	8
Markers	2	9	12	23	4	27

Finally it should be noted that among the specific abnormalities was one case of acute promyelocytic leukemia (APL) and t(15;17) occurring in a patient treated with localized radiation for cervical cancer (case 46).

Trisomy 8 was found in only 4 cases.

On examining the correlation between the types of chromosome abnormalities and previous exposure to hazard (Table 6), a certain number of observations can be made. Loss of chromosome #7 occurs more often after lymphomas (10/18) than after solid tumors (4/25) ($p < 0.05$), thus, it also seems to be related to the nature of former treatment (chemotherapy plus radiotherapy). On the other hand, abnormalities of chromosome #17 appear to be more frequent following solid tumors than after lymphomas (7/25 and 1/18).

The occurrence of chromosome #17 defects is also higher in patients exposed to

Table 7 Cytologic classification of 63 patients

AL (≥ 30% blast cells) (47 cases)			MDS (< 30% blast cells) (16 cases)		
FAB		Unclass	FAB		Unclass
M1	5	13	RA-S	1	8
M2	13		RAEB	3	
M3	1		RAEB-T	2	
M4	10		CMML	2	
M5	3				
M6	2				
Total	34		Total	8	

professional hazards (5/8) than in cases of therapeutic exposure (9155). No correlation was found for chromosome #5 defects (−5 and 5q−).

The results of the cytologic study are shown in Table 7. Forty-seven cases were classified as acute leukemia (medullary blasts ≥30%) and 16 cases as DMS (medullary blasts <30%). We were unable to classify all of the cases unambiguously according to the FAB system [4, 5]. Thirteen cases of acute leukemia were unclassifiable because of the hypocellularity of the medullary aspirate and/or the existence of cytologic variation, This cytologic variation was defined [6] as the presence of several precursors (blasts) and/or more mature elements in at least three cell lines.

Among the DMS cases, there were eight cases corresponding to atypical blood disorders that did not satisfy the criteria for the various forms of refractory anemia, with or without excess blasts [5]. Attempts at classification also were hindered, in part, by the hypocellularity of the medullary aspirates.

A correlation was found between the presence of micromegakaryocytes and/or macroplatelets and monosomy 7 ($p < 0.01$), but none between these cytologic abnormalities and chromosome #5 defects (monosomy 5 and 5q−) or the 7q− defect.

A correlation was also found between chromosome variation and cytologic variation ($p < 0.051$.

DISCUSSION

Secondary nonlymphoid blood disorders are relatively rare compared with primary leukemia and DMS; furthermore, numerous difficulties are encountered in studying them. This may account for the limited number of series with chromosome studies in the literature [1, 10, 11]. Therefore, we deemed it useful *to* assemble a series of 63 cases in which the chromosomes and cytology were reviewed within the framework of a cooperative study, with a certain homogeneity in the methods of analysis.

The results of our study confirm certain established data concerning ANLL secondary to treated and cured malignant lymphoma [12]: there is a high proportion of chromosome abnormalities, found in 56 of 63 cases (88.9%); widespread occurrence of hypodiploidy (50.8%); complex abnormalities (42.9%); and defects of chromosome #5 (39.7%), #7 (46%), and #17 (22.2%). However, chromosome #3 was rarely involved, as opposed to what has been suggested by other investigators [1]. Thus, the ensemble of abnormalities observed confirms that there are notable differences between the chromosome abnormalities occurring in secondary leukemia and DMS, as opposed to those in primary leukemia and DMS. It should be noted that chromosome #8 rarely was implicated in secondary blood disorders. This reinforces the specific nonrandomness of chromosome abnormalities in secondary leukemia compared with primary leukemia.

The classification of chromosome abnormalities in terms of etiology and, thus, with respect to type of carcinogenic hazards, gives interesting results.

Monosomy 7 appears with great frequency in leukemic patients previously treated for malignant lymphoma (10 cases) than in those formerly treated for cancer (4 cases). Chromosome #5 abnormalities occur with equal frequency in both groups. However, chromosome #17 involvement seems more common following cancer than lymphoma. These differences may reflect variations in treatment, which more commonly included localized radiotherapy for cancer patients.

Chromosome #17 seems more often involved in blood disorders occurring after exposure to professional hazards (5/8) than following malignancy (9/55). However, there is no obvious correlation between "chromosome variation" and the type of exposure to leukemogenic hazards.

The appearance of different types of chromosome abnormalities following different courses of treatment should be compared with studies showing that the chro-

mosome abnormality profile in ANLL varies depending on whether or not the patient has been exposed to professional leukemogenic hazards [13, 14]. Indeed, the specificity of chromosome abnormalities for a given carcinogen has been experimentally demonstrated in rats [15].

The present study confirms that cytogenetic and cytologic "variations" are related [6], which in turn suggests that the multiplicity of chromosome abnormalities is correlated with the involvement of several blood lines and, in part, may account for the difficulties encountered in classifying certain secondary ANLL according to the FAB system. The link between the presence of micromegakaryocytes and/or macroplatelets and the presence of monosomy 7 [6] also was confirmed. However, no correspondence was found between abnormalities of chromosomes #17 and #5, particularly the 5q− defect, which may suggest that the 5q− defect is, on the whole, different in secondary ANLL and in anemic syndromes with chromosome abnormality [16].

The search for further correlations is rendered difficult by the relative scarcity of secondary blood disorders. The increasing frequency of such ailments makes it all the more important to extend this type of investigation in order to explore the connection between chromosome abnormalities and etiologic factors, be they professional or therapeutic.

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