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CHROMOSOME ABNORMALITIES IN PATIENTS WITH CHRONIC MYELOCYTIC LEUKEMIA

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Abstract. Fifty patients with chronic myelocytic leukemia (CML) grouped into four stages on the basis of clinical and hematological results were analyzed with chromosomal banding techniques. Of the 50 patients, 48 had the "standard" type of Ph^1 translocation, t (9 ; 22) (q34; q11) and the remaining 2 had Ph^1-negative diploid karyotype. The frequency of numerical chromosomal changes and/or structural chromosomal changes other than the Ph^1 translocation varied with the stages; the frequency was 1 of 28 cases (3.6%) for patients in stage I (chronic phase), 5 of 11 (45.5%) in stage II (early stage of blastic phase), 11 of 13 (84.6%) in stage III (blastic phase) and 2 of 7 (28.6%) in stage IV (remission phase). Numerical changes in hyperdiploid leukemic cells correlated well with the appearance of extra ♯8 and extra Ph^1. In 5 cases with hypodiploid leukemic cells, one of the ♯7 pair was absent in 4 cases and Y in 1 case. As structural changes, partial excess of chromosome 1, isochromosome 17q, isochromosome 1q, tdic (20p+ ; 21q−), del (7) (q11), t (2p+ ; 11p−), ♯12q+ and Xp+ were observed. Chromosomal analysis alone is not the best marker to diagnose the onset of blastic phase; however, it is a useful parameter when considered in combination with clinical and hematological results.

Key words: Ph^1-positive chronic myelocytic leukemia, Ph^1-negative chronic myelocytic leukemia, chromosome abnormalities, chronic phase, early stage of blastic phase, blastic phase.

Chronic myelocytic leukemia (CML) has some specific characters: a) Ph^1 translocation is frequent, b) blastic crisis generally occurs in the course of the disease and c) patients generally die in the course of blastic crisis. Because therapeutic approaches are ineffective and survival time is very short once the disease reaches the blastic phase, it is important to diagnose the onset of the blastic phase. The present study reports the results of chromosomal analysis to diagnose the onset of the blastic phase in 50 patients with CML. CML was grouped into the following four stages: (stage I) cases in the chronic phase, (stage II) cases satisfing more than one parameter of Kitazima's criteria for early diagnosis of blastic crisis (1), (stage III) cases with clearly recognized hiatus leukemicus, and (stage IV) cases in remission.

MATERIALS AND METHODS

The 50 patients (age 21 to 80 years) included in this study were followed in the Division of Pathology, Cancer Institute, and in the 2nd Department of Internal Medicine at the Okayama University Medical School from January 1979 to June 1980. Bone marrow (BM) aspirates (0.5–1.0 ml) and peripheral (5–10 ml) blood cells (Bl) were used for chromosomal examinations. BM cells were dispersed in 10 ml RPMI 1640 medium containing 20% bovine serum and 0.4% lactoalbumin or McCoy 5a medium containing 10% fetal calf serum, then cultured at 37°C for about 24 h in 5% CO_2 in an air atmosphere. Mitotic cells were arrested with Colcemid at 0.5 μg/ml for 2–3 h and metaphase cells were treated with 0.075 M KCl hypotonic solution for 13 min at 37°C. Usually, slides were made according to a routine air-dry method immediately after the fixation. For banding studies, the Q-, G-, C- and R-banding methods were used (2–5). Peripheral blood samples obtained from some patients were processed under the same conditions as BM specimens and cultured for 24 or 48 h without phytohemagglutinin (PHA). In all cases, 50 mitotic cells were counted, and at least another 10 cells were photographed and analyzed with banding. Chromosomes were identified and karyotypes were expressed according to the Paris nomenclature (6).

RESULTS

Fifty patients with CML grouped into four stages on the basis of the clinical and hematological results were analyzed by chromosomal banding techniques. Of the 50 patients, 48 had the "standard" type of Ph^1 translocation, t (9 ; 22) (q34 ; q11) and the remaining 2 had a Ph^1-negative diploid karyotype. The frequency of numerical chromosomal changes and/or structural chromosomal changes other than the Ph^1 translocation varied with stages.

Chromosomal and other pertinent data in stage I (the chronic phase) are given in Table 1. Twenty-seven of the 28 cases were Ph^1-positive and one was Ph^1-negative. All cases had a modal chromosome number of 46. One case had a clone with chromosome abnormalities (24%) in addition to the major leukemic clone of the "standard" type of Ph^1 translocation. Chromosomal abnormalities other than Ph^1 occurred in 1 of 28 cases (3.6%). The abnormal karyotype was 46, X, Yq−, Ph^1/45, X, Yq, −7, Ph^1 (24%). This patient advanced to the blastic phase two months later.

Of the 11 cases in stage II (the early stage of the blastic phase), Ph^1 translocation only was observed in 6 cases, numerical or structural changes other than Ph^1 were seen in 4 cases, and Ph^1-negative was present in 1 case. The distribution of the chromosome numbers in the 11 cases is given in Table 2. Of the 11 cases, 10 had only one modal number and 1 bimodal. Of the 10 cases with only one mode, 9 had a diploid mode and 1 a hyperdiploid mode. The case with bimodal chromosome distribution had both hyperdiploid and diploid modes. Chromosomal, clinical and hematological data are shown in Table 3. Of 11

TABLE 1. KARYOTYPES OF PATIENTS WITH CML IN THE STAGE I.

Case no.	Patient	**Age/Sex	Date of diagnosis	Date of chromosome analysis	Material	Modal chromosome number	Karyotype
*1	S. S.	29/M	78. 12. 19.	79. 1. 18.	Bl***	46(19)	46, XY, Ph^1
*2	E. I.	46/F	78. 5. 22.	79. 2. 1.	BM****	46(50)	46, XX, Ph^1
3	A. M.	57/M	78. 4. —	79. 2. 2.	BM	46(12)	46, XY, Ph^1
*4	H. S.	50/M	77. 1. 26.	79. 2. 15.	BM	46(21)	46, XY, Ph^1
5	K. A.	42/F	78. 8. 23.	79. 3. 22.	BM	46(13)	46, XX, Ph^1
				79. 6. 23.	BM	46(15)	46, XX, Ph^1
6	K. M.	28/M	79. 3. 29.	79. 4. 28.	BM	46(24)	46, XY, Ph^1
7	Y. T.	39/M	79. 4. 11.	79. 5. 17.	BM	46(28)	46, XY, Ph^1
*8	I. Y.	47/M	72. 8. 21.	79. 5. 26.	BM	46(37)	46, X, Yq−, Ph^1
				79. 11. 14.	BM	46(20)	46, X, Yq−, Ph^1/45, X, Yq−, Ph^1, −7 (24%)
9	T. K.	43/M	79. 5. 30.	79. 6. 4.	BM	46(19)	46, XY, Ph^1
10	K. T.	47/F	79. 6. 30.	79. 6. 30.	BM	46(10)	46, XX, Ph^1
*11	T. H.	52/M	79. 6. 20.	79. 7. 4.	BM	46(10)	46, XY, Ph^1
12	H. F.	64/F	77. 5. 10.	79. 8. 6.	BM	46(17)	46, XX, Ph^1
13	M. K.	41/M	79. 9. 14.	79. 9. 21.	BM	46(20)	46, XY, Ph^1
14	K. N.	45/M	74. 1. 16.	79. 9. 26.	BM	46(10)	46, XY, Ph^1
15	T. N.	47/F	78. 9. 4.	79. 10. 13.	BM	46(10)	46, XX, Ph^1
16	S. A.	37/M	79. 10. 12.	79. 10. 23.	BM	46(15)	46, XY, Ph^1
17	Y. I.	42/M	79. 9. 21.	79. 11. 9.	BM	46(20)	46, XY, Ph^1
18	H. M.	62/M	78. 1. 25.	79. 11. 21.	BM	46(16)	46, XY, Ph^1
19	S. S.	54/M	75. 2. 21.	79. 11. 21.	BM	46(13)	46, XY, Ph^1
20	H. O.	26/M	79. 12. 5.	79. 12. 6.	BM	46(13)	46, XY, Ph^1
21	M. N.	33/M	78. 5. 8.	79. 12. 8.	BM	46(12)	46, XY, Ph^1
22	H. K.	30/M	78. 10. 19.	79. 12. 8.	BM	46(10)	46, XY, Ph^1
23	M. F.	51/M	78. 11. 2.	79. 12. 8.	BM	46(10)	46, XY, Ph^1
24	K. U.	51/F	80. 1. 23.	80. 1. 23.	BM	46(10)	46, XX, Ph^1
25	K. K.	39/F	79. 12. 11.	80. 2. 7.	BM	46(10)	46, XX, Ph^1
26	M. K.	54/M	80. 3. 13.	80. 3. 19.	BM	46(10)	46, XY, Ph^1
27	M. U.	49/M	80. 3. 19.	80. 3. 28.	Bl	46(15)	46, XY, Ph^1
28	U. M.	58/F	77. 2. —	80. 6. 9.	BM	46(15)	46, XX

Stage I=chronic phase. Number in parentheses=number of banded cells examined. *Cases No. 1 and 2 also were examined for chromosome analysis in stage II, cases No. 8 and 11 in stage III and case No. 4 in stage III and IV. **Age of patient when chromosome analysis was made. ***Bl=blood, ****BM=bone marrow.

TABLE 2. CHROMOSOME NUMBER DISTRIBUTION OF PATIENTS WITH CML IN THE STAGE II.

Case no.	Patient	**Age/Sex	Date of diagnosis	Date of chromosome analysis	Material	Chromosome distribution									
						44	45	46	47	48	49	50	51	4n≦	Total
1.	T. O.	47/F	78. 4.—	79. 2.27.	BM		3[a]	42(44)						5	50(44)
*2.	S. S.	63/M	77. 1.26.	79. 3. 5.	BM			50(18)							50(18)
				79. 9. 7.	BM		5(3)	44(27)						1	50(30)
3.	H. A.	45/F	62.—	79. 3. 8.	Bl			50(22)							50(22)
4.	S. S.	29/M	78.12.19.	79. 4.19.	BM		1	49(32)							50(32)
5.	I. Y.	21/F	75.10. 9.	79. 6.18.	BM								49(22)	1	50(22)
6.	Y. U.	77/M	77.11.12.	79. 6.25.	BM			42(25)	2(2)			4(3)		2	50(30)
*7.	E. I.	46/F	78. 5.22.	79. 7. 2.	BM			48(10)						2	50(10)
8.	K. M.	80/F	74. 1.19.	79. 9. 1.	BM		2[a]	48(18)							50(18)
9.	S. F.	22/M	77. 8.16.	79. 9. 6.	Bl			24(6)		26(4)					50(10)
10.	S. O.	46/M	79. 8. 8.	79.10.11.	BM		1	46(10)						3	50(10)
11.	K. F.	54/M	77. 7.—	79.10.19.	BM		3[a]	47(10)							50(10)

Stage II=early stage of blastic phase. Number in parentheses=number of banded cells examined. [a] Random chromosome loss, presumably due to cell breakage. *Cases 2 and 7 were examined for chromosome analysis in the stage I. **Age of patient when chromosome analysis was made. Bl=blood, BM=bone marrow.

TABLE 3. RESULTS OF CHROMOSOMAL, CLINICAL AND/OR HEMATOLOGICAL DATA IN THE STAGE II.

Case no.	Patient	Karyotype	Clinical and/or hematological data suggesting early stage of blastic crisis
1.	T. O.	46, XX, Ph^1/46, XX, Ph^1, t (2 ; 11) (p25 ; p12)	Mybl : 8.0% (Bl), 5.2% (BM), Promy : 24% (Bl), 33.8% (BM), Plts : 334×10^4
*2.	S. S.	46, XY	Mybl : 5.6% (BM), Promy : 20.0% (BM)
		46, XY/45, XY, −7	Mybl : 6.4% (BM), RBC : 265×10^4, CRP : (+)
3.	H. A.	46, XX, Ph^1	Huge splenomegaly, Dry tap (BM)
4.	S. S.	46, XY, Ph^1	Huge splenomegaly, Promy : 29.4% (BM), WBC 80, 600, Neuralgic pain
5.	I. Y.	51, XX, Ph^1, +8, +9, +14, +19, + Ph^1	Huge splenomegaly, Mybl : 13% (Bl), RBC : 220×10^4, Dry tap (BM), CRP : 2(+)
6.	Y. U.	46, XY, Ph^1/47, XY, Ph^1, +8/50, XY, Ph^1, +i (1q), +8, +13, + Ph^1	Huge splenomegaly, Mybl : 7.8% (BM), RBC : 289×10^4, Neuralgic pain
*7.	E. I.	46, XX, Ph^1	Huge hepatomegaly, Mybl : 7.6% (BM), Promy : 30% (BM)
8.	K. M.	46, XX, Ph^1	Huge splenomegaly, Mybl : 7.2% (BM), Promy : 30% (BM)
9.	S. F.	46, XY, Ph^1/48, XY, Ph^1, +8, + Ph^1	Dry tap (BM), Plts : 8.5×10^4, CRP : 3 (+)
10.	S. O.	46, XY, Ph^1	Mybl : 10% (BM), CRP : (±)
11.	K. F.	46, XY, Ph^1	Splenomegaly, Mybl : 5.6% (BM), Promy : 23.2% (BM), CRP : (+)

* Cases No. 2 and 7 were examined for chromosome analysis in the stage I.

cases, 7 advanced to stage III a few months after being examined for chromosome analysis. The remaining 4 cases died unexpectedly before reaching the stage III. Numerical chromosomal changes and/or structural chromosomal changes other than the Ph^1 translocation were found in 5 of 11 cases (45.5%). Some of the cases in stage II having karyotypic abnormalities are described below in detail.

Case 1 (T. O., female) had a sharp mode of 46 in the chromosome number. Forty of 44 cells with the mode of 46, which were studied with the banding techniques, had a karyotype of 46, XX, Ph^1, t (2 ; 11) (p25 ; p12) ; whereas the remaining 4 cells had the "standard" type Ph^1 chromosome.

Although case 2 (S. S., male) revealed Ph^1-negative metaphase on March 5, 1979, chromosomal changes were present on September 7, 1979, in bone marrow cells. The modal chromosome number was 46. Twenty-seven of 30 cells with the mode of 46, which were studied with Q-, G-, R- and C-banding techniques, had a normal karyotype of 46, XY, whereas the remaining 3 cells had hypodiploid cells, *i.e.*, the karyotype was 45, XY, -7 (Fig. 1).

Case 5 (I. Y , female) had a sharp mode of 51 in the chromosome number. The karyotype was 51, XX, Ph^1, $+8$, $+9$, $+14$, $+19$, $+Ph^1$ (Fig. 2). The two Ph^1 chromosomes were morphologically identical, but 2 chromosomes consisting of trisomy of chromosome 9 were of normal type and the remaining 1 was of t9q+ translocated from one of the Ph^1's chromosomes.

In case 6 (Y. U., male), the chromosome number ranged from 46 to 50 with a modal number of 46. Twenty-five of 30 cells with the mode of 46, which were studied with banding techniques, had a karyotype of 46, XX, Ph^1 ; whereas the remaining cells had somewhat different chromosome constitutions, *i.e.*, 47, XY, Ph^1, $+8$ in 2 cells and 50, XY, Ph^1+8, $+13$, $+Ph^1+i$ (1q) in 3 cells. The extra i (1q) was an isochromosome formed by the centromeric fusion of two 1q arms.

Case 9 (S. F., male) had bimodal distribution of 46 and 48 in chromosome number. Of the cells with a modal of 46, which were studied with the banding techniques, 6 cells all had a karyotype of 46, XY, Ph^1. On the other hand, four of 48 modal cells all had a karyotype of 48, XY, Ph^1, $+8$, $+Ph^1$.

Of the 13 cases in stage III (clearly recognized hiatus leukemicus), 11 had numerical or structural changes in addition to the Ph^1 translocation (84.6%) and 2 had only the "standard" type of Ph^1 translocation t (9q+ ; 22q−). Chromosomal and other pertinent data are shown in Tables 4 and 5. The distribution of the chromosome numbers were single sharp modal numbers. Of the 11 cases with single modes, 7 had a diploid mode, 3 were hypodiploid and 1 was hyperdiploid. Another 2 cases had nearly bimodal distribution. Structural or numerical changes were found in the following decreasing order: partial excess of

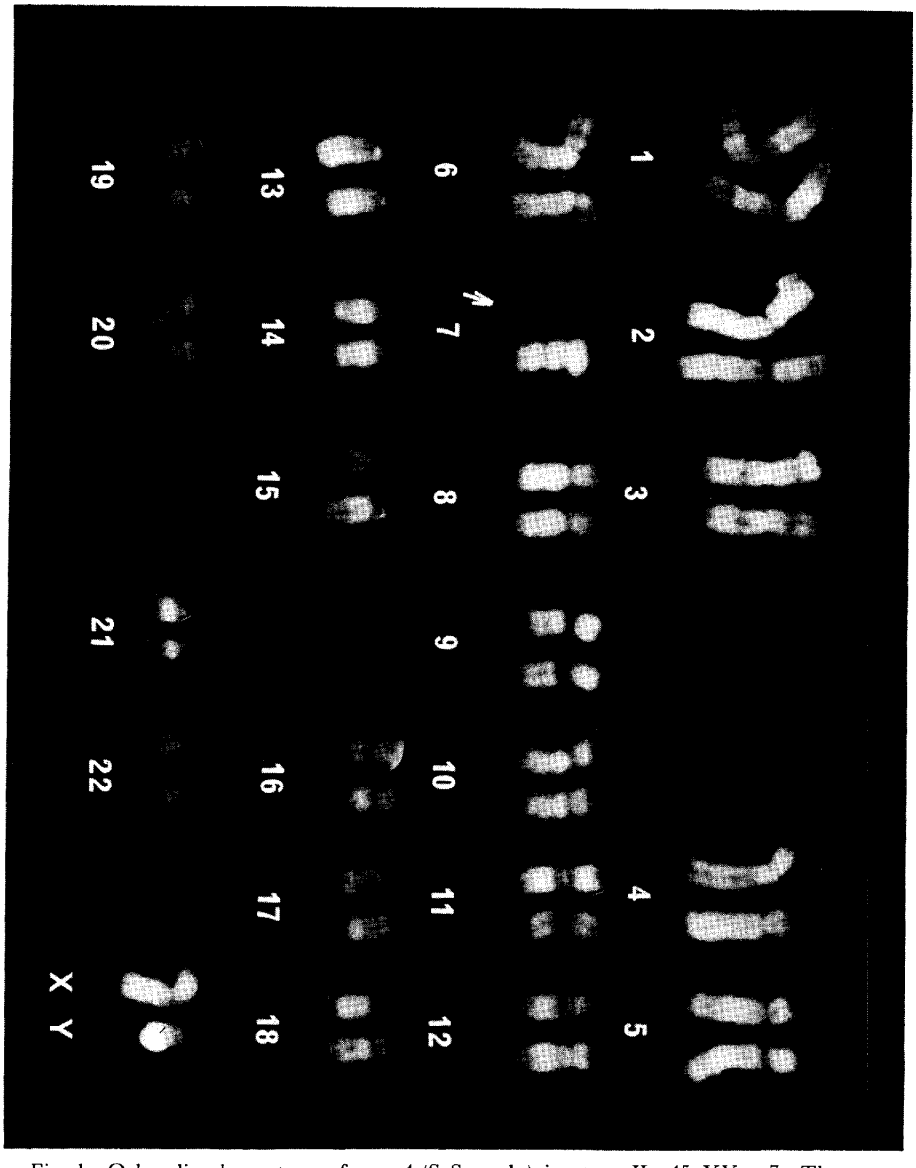


Fig. 1. Q-banding karyotype of case 4 (S. S., male) in stage II : 45, XY, −7. The arrow indicates the missing chromosome 7.

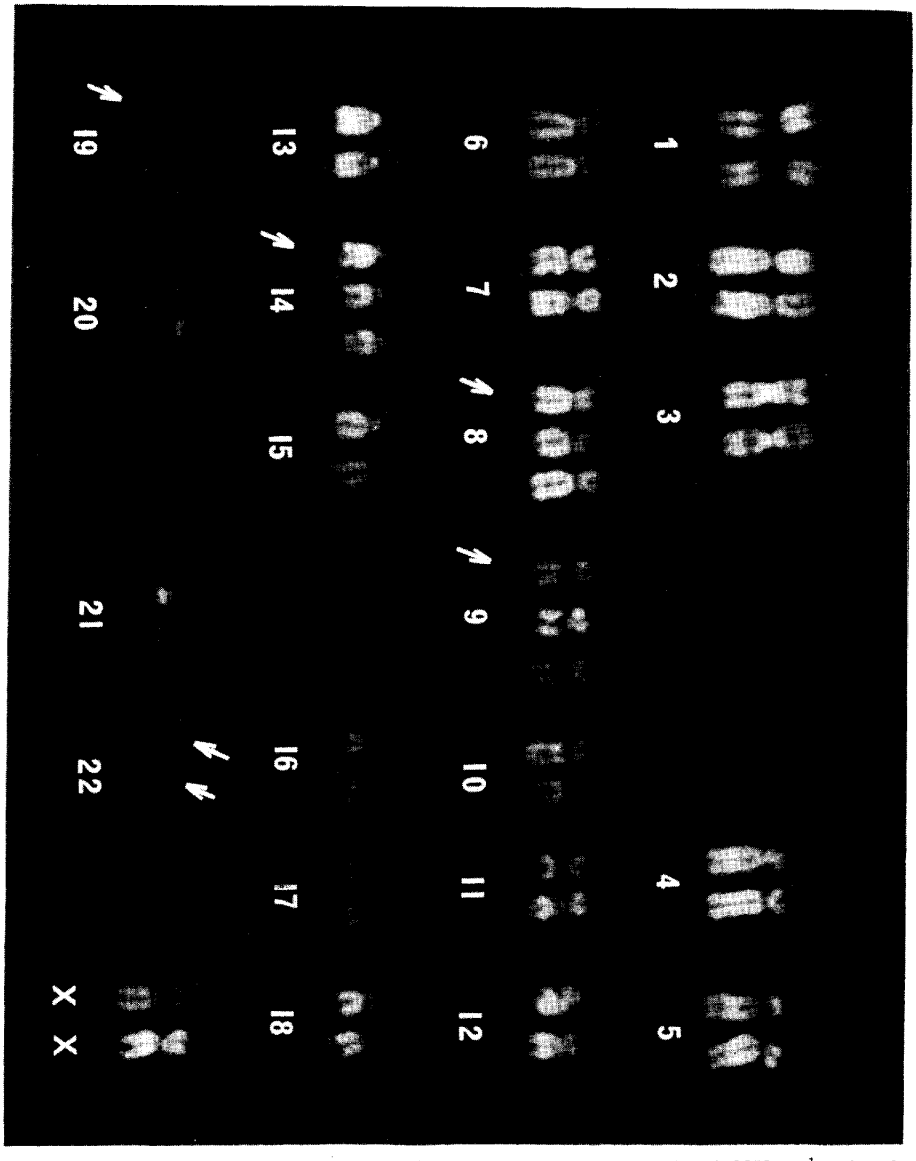


Fig. 2. Q-banding karyotype of case 6 (I. Y., female) in stage II: 51, XX, Ph^1, +8, +9, +14, +19, +Ph^1. Arrows indicate one "standard" Ph^1 translocation, 3 trisomies and a second Ph^1.

TABLE 4. CHROMOSOME NUMBER DISTRIBUTION OF PATIENTS WITH CML IN THE STAGE III.

Case no.	Patient	**Age/Sex	Date of diagnosis	Date of chromosome analysis	Material	Chronomosome distribution									
						44	45	46	47	48	49	58	59	4n≦	Total
*1.	S. A.	44/M	75. 8. —	79. 1. 16.	Bl***	1	4	45(26)							50(26)
2.	S. N.	40/M	74. 10. 8.	79. 2. 8.	BM****			47(37)						3	50(37)
*3.	M.M.	69/F	75. 9. 25.	79. 3. 16.	BM		1	46(24)	1					2	50(24)
				79. 8. 8.	BM			47(13)						3	50(13)
4.	Y. Y.	53/F	79. 4. 4.	79. 9. 4.	BM	2	2(2)	45(16)						1	50(18)
5.	T. T.	47/M	76. 8. 19.	79. 9. 4.	BM		50(18)								50(18)
				79. 12 27.	BM		14(3)			4	32(17)				50(20)
*6.	I. Y.	47/M	72. 8. 21.	80. 1. 11.	BM		43(10)	7(5)							50(15)
*7.	H. S.	51/M	77. 1. 26.	80. 1. 11.	BM		42(15)	8(10)							50(25)
8.	Y. H.	21/F	77. 6. —	80. 1. 26.	BM	1		49(15)							50(15)
*9.	T. H.	53/M	79. 6. 20.	80. 1. 30.	Bl				50(25)						50(25)
*10.	T. T.	51/M	78. 1. 24.	80. 3. 8.	BM		35(15)	15(13)							50(28)
11	Y. S.	28/M	77. 12. 26.	80. 4. 15.	BM		2	28(10)	17(4)	3(1)					50(15)
12.	M. F.	44/F	77. 10. —	80. 5. 9.	Bl			49(15)						1	50(15)
13	K. K.	29/F	76. 9. —	80. 5. 15.	BM			3(1)				3	36(20)	8	50(21)

Stage III=blastic phase. Number in parentheses=number of banded cells examined. * Cases no. 6, 7 and 9 were examined for chromosome analysis in stage I, case no. 1, 3, and 10 also in stage IV. ** Age of patient when chromosome analysis was made. Bl***=blood, BM****=bone marrow.

TABLE 5. SUMMARY OF CHROMOSOMAL DATA IN THE STAGE III

Case no.	Patient	Karyotype
*1.	S. A.	46, XY, Ph^1/46, XY, Ph^1, −6, +t (1;6) (q25;q25)/46, XY, Ph^1, −15, +t (1;15) (q12;p11)
2.	S. N.	46, XY, Ph^1
*3.	M. M.	46, XX, Ph^1/46, XX, Ph^1, −4, +t (1;4) (q22;q31), del (7) (q11) 46, XX, Ph^1/46, XX, Ph^1, −4, +t (1;4) (q22;q31), del (7) (q11)
4.	Y. Y.	46, XX/46, XX, Ph^1/45, XX, Ph^1, −4
5.	T. T.	45, X, −Y, Ph^1 45, X, −Y, Ph^1/49, X, −Y+2t (9;22) (q34;q11), +8, +12
*6.	I. Y.	45, X, Yq−, Ph^1, −7/46, X, Yq−, Ph^1
*7.	H. S.	45, XY, Ph^1, −7/46, XY, Ph^1
8.	Y. H.	46, XX, Ph^1, /46, XX, Ph^1, i (17q)
*9.	T. H.	47, XY, Ph^1, +8, i (17q)
*10.	T. T.	46, XY, Ph^1, /45, XY, ph^1, −9, −20, −21, +tdic (20;21) (p13;q22), +mar
11.	Y. S.	46, XY, Ph^1/46, XY, Ph^1, i (17q)/47, XY, Ph^1, +Ph^1/48, XY, Ph^1, +Ph^1, +8, i (17q)
12.	M. F.	46, XX, Ph^1
13.	K. K.	46, XX, Ph^1/59, Xp+, −X, Ph^1, +4, +6, +6, t (7;?) (p15;?), +t (7;?) (p15;?), +8, +8, +12q+, +17, +19, +19, +21, +22, +Ph^1, +Ph^1

* Cases no. 6, 7 and 9 were examined for chromosome analysis in the stage I, cases no. 1, 3, and 10 also in stage IV.

TABLE 6. KARYOTYPES OF PATIENTS WITH CML IN THE STAGE IV

Case no.	Patient	**Age/Sex	Date of diagnosis	Date of chromosome analysis	Material	Modal chromosome number	Karyotype
*1.	S. A.	44/M	75. 8. —	79. 3. 2.	BM****	46(15)	46, XY, Ph^1
*2.	M. M.	69/F	75. 9. 25.	79. 4. 9.	BM	46(35)	46, XX, Ph^1
3.	G. T.	26/M	76. 11. 20.	79. 4. 21.	BM	46(15)	46, XY, Ph^1
				79. 10. 17.	BM	46(19)	46, XY, Ph^1
4.	T. T.	46/M	78. 8. 10.	79. 9. 5.	BM	46(50)	46, XY, Ph^1/50, XY, Ph^1, +2C, +D, +Ph^1 (6%)
5.	S. N.	72/M	78. 8. 24.	79. 8. 15.	BM	46(12)	46, XY, Ph^1
*6.	H. S.	50/M	77. 1. 26.	80. 3. 6.	BM	46(12)	46, XY, Ph^1/45, XY, Ph^1, −7 (10%)
*7.	T. T.	51/M	78. 1. 24.	80. 5. 13.	BM	46(15)	46, XY, Ph^1

Stage IV=remission phase. Number in parentheses=number banded cells examined. *Cases no. 1, 2 and 7 also were examined for chromosome analysis in stage III, case no. 6 in stages I and III. ** Age of patient when chromosome analysis was made. **** BM=bone marrow.

chromosome 1, iso-17q, tdic (20p+ ; 21q−), ♯9q+, ♯12q+ and Xp+ and an extra Ph^1, ♯8, ♯4, ♯6, ♯17, ♯19, ♯20 and missing of ♯7, Y and ♯4. Some of the cases having karyotypic abnormalities are described below in detail.

In case 1 (S. A., male), chromosome analysis was performed in stage IV (remission phase) and stage III (second blastic phase). In stage IV, the "standard" type Ph^1 translocation was present; however, some additional chromosome abnormalities other than the Ph^1 developed in the second blastic phase. Three of 26 banded cells had 46, XY, Ph^1, 17 of them 46, XY, −6, +t (1 ; 6) (q25 ; q25) and 6 of them 46, XY, Ph^1, −15, +t (1 ; 15) (q21 ; p11).

In the specimens obtained from case 3 (M. M., female) on March 16, 1979 (blastic phase) and August 8, 1979 (second blastic phase), cells with the same chromosomal abnormalities other than the Ph^1 translocation were present, *i.e.*, 46, XX, Ph^1, −4, +t (1 ; 4) (q22 ; q31), 7q−.

The modal chromosome number in case 4 (Y. Y., female) was 46. Of 18 banded cells, one cell revealed normal karyotype 46, XX, 15 cells 46, XX, Ph^1 and 2 cells 45, XX, Ph^1, −4. The proximal portion of one of the chromosome 13 pairs in each of the cells was strongly bright with Q-banding stain.

Although examination in the stage III of case 5 (T. T., male) on September 4, 1979, revealed a missing Y, additional chromosome changes were observed in bone marrow cells when a second examination was made on December 27, 1979. The karyotype was 49, X, −Y, +8, +2t (9 ; 22) (q34 ; q11), +12.

In case 6 and case 7 (I. Y., male and H. S., male), the initial examination during the chronic phase revealed a "standard" Ph^1; however, hypodiploid cells were present after patients had advanced to stage III. In both cases, the karyotype was 45, XY, Ph^1, −7.

The initial examination in the chronic phase of case 9 (T. H., male) revealed a "standard" Ph^1 translocation without any additional abnormalities. In the specimen obtained on January 30, 1980, after the patient had advanced to stage III, hyperdiploid cells were present. The karyotype was 47, XY, Ph^1, +8, i (17q).

Case 10 (T. T., male) had two clones of leukemic cells: a clone of 46, XY, Ph^1 and a clone of 45, XY, Ph^1, −9, −20, −21, +tdic (20 ; 21) (p13 ; q22), +mar (Fig. 3). The marker chromosome appears to have mainly originated from two 9q.

The chromosome numbers were distributed from 45 to 48 in case 11 (Y. S., male). Of 15 banded cells, 3 cells revealed 46, XY, Ph^1, 7 cells 46, XY, Ph^1, i (17q), 4 cells 47, XY, Ph^1, +Ph^1 and 1 cell 48, XY, Ph^1, +8, i (17q), +Ph^1.

The chromosome number in case 13 (K. K., female) ranged from 46 to 59 with a modal number of 59. Of 21 banded cells, 1 cell revealed 46, XX, Ph^1 and 20 cells 59, Xp+, −X, Ph^1, +4, +6, +6, t (7 ; ?) (p15 ; ?), +t (7 ; ?) (p15 ;

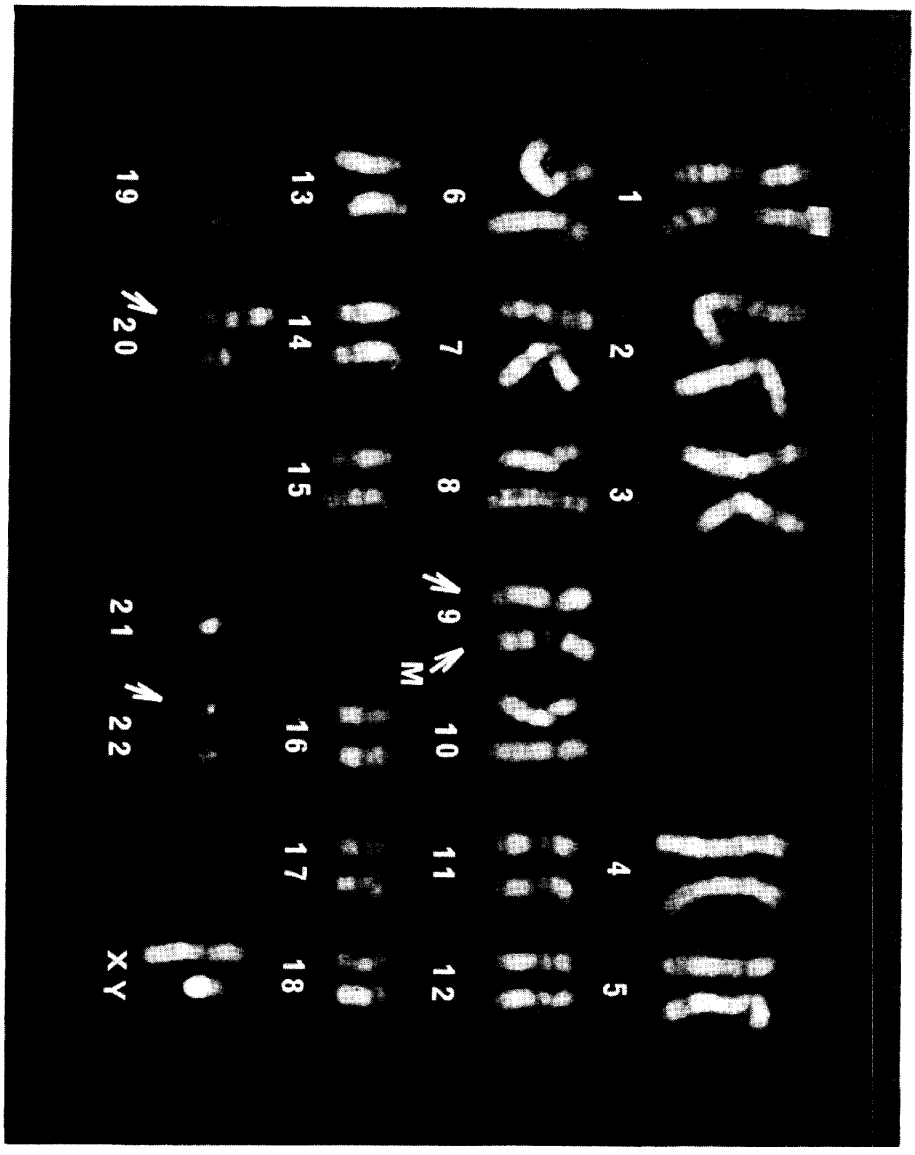
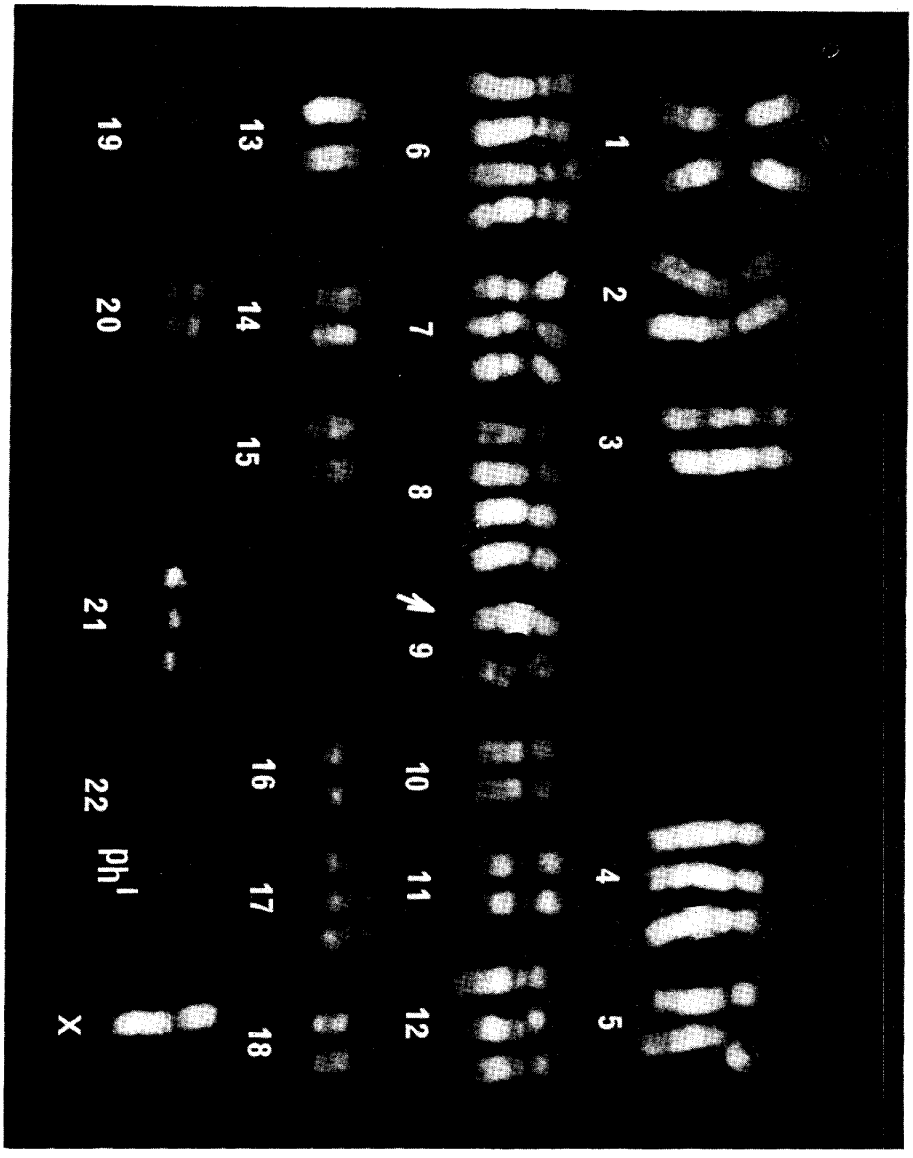


Fig. 3. Q-banding karyotype of case 10 (T. T., male) in stage III : 45, XY, Ph^1, −9, −20, −21, +tdic (20 ; 21) (p13 ; q22), +mar. Arrows indicate the Ph^1 translocation between chromosomes 9 and 22 and abnormal chromosomes.



Pig. 4. Q-banding karyotype of case 13 (K. K., female) in stage III: 59, Xp+, −X, Ph^1, +4, +6, +6, t(7;?) (p15;?), +t(7;?) (p15;?), +8, +8, +12q+, +17, +19, +19, +21, +22, +Ph^1, +Ph^1. The arrow indicates the Ph^1 translocation between chromosomes 9 and 22.

?), +8, +8, +12q+, +17, +19, +19, +21, +22, +Ph^1, +Ph^1 (Fig. 4). The banding patterns of these Ph^1 chromosomes were typical; only one of the chromosome 9 pair had the "standard" type of Ph^1 translocation. Extra chromosomal bands were observed on the short arm of X chromosome (Xp+) and on the long arm of chromosome 12 (12q+) but their origin could not be determined.

Chromosomal and other pertinent data for stage IV (remission) are given in Table 6. In cases 4 and 6, a small percentage of clones with chromosomal abnormalities remained in addition to the major leukemic clone with the "standard" type of Ph^1 translocation. In other cases, only Ph^1-positive cells remained.

DISCUSSION

In the chronic phase of CML, chromosomal abnormalities other than the Ph^1 translocation were sometimes observed in bone marrow and blood cells (7). Sonta *et al.* demonstrated that, of the 57 cases, 15 cases (26.3%) had chromosomal changes other than the Ph^1; the appearance of i (17q), −7, +8 and +Ph^1 being most frequent (8). These changes are the ones usually encountered when CML develops into the blastic phase (9). In the present study, 1 (3.6%) of the 28 cases of chronic phase had chromosomal abnormalities other than the Ph^1 translocation. Chromosomal abnormalities other than the "standard" type Ph^1 in our cases of stage I (chronic phase) were fewer than in Sandberg's reports (27%) (7). This may have been due to the division of CML into 4 stages by Kitazima's criteria (1) in our study. In stage II, 6 of the 11 cases had only the "standard" type of Ph^1 translocation, 4 had numerical and/or structural changes other than the Ph^1 translocation and 1 had Ph^1-negative cells, in which case a few cells with a hypodiploid nature, *i.e.*, 45, XY, −7 appeared at the second examination (Table 2). Mintz *et al.* reported that 2 of 10 cases of Ph^1-negative CML showed evolution of karyotypes involving trisomy No. 8 in the blastic phase. One case involved t (6q− ; 14q+) initially (10). Numerical chromosomal changes appeared to involve −7, +8, +9, +13, +14, +19 and +Ph^1. Structural chromosomal abnormalities were observed in two cases: a translocation between chromosomes 2 and 11, *i.e.*, t (2p+ ; 11p−) in one case and isochromosome 1q in another case. The most common chromosomal changes in stage III were extra Ph^1, extra chromosome 8 and an isochromosome 17q as others have reported (9). In stage II and III, an extra chromosome 8 appeared in 7 of 24 cases (29.1%), an extra Ph^1 in 6 (25.0%) and isochromosome 17q in 3 (12.5%). Two of 13 cases in stage III had chromosomal abnormalities including partial trisomy of chromosome 1. Rowley reported duplication of 1q25-1q32 in 34 patients with various hematological disorders including acute leukemia, polycythemia vera and myelofibrosis (11). Recently, duplication of the

long arm of chromosome 1 has also been reported for myeloproliferative disorders (12), non-endemic Burkitt's lymphoma (13) and Japanese Burkitt's lymphoma (14). The formation of marker chromosomes involving the long arm of chromosome 1 may play an important role in proliferation of the affected cell. In our 50 cases, there were 5 hypodiploid cases; 1 was in stage I, 1 in stage II and 3 in stage III. One case in stage I proceeded to a blast crisis 2 months later. Therefore all 5 cases were related to a blast crisis. Four of 5 hypodiploid cases had a karyotypes with monosomy 7 and one had a missing Y. In a case report, Ronald M *et al.* demonstrated the emergence of a cell with extreme hypodiploidy in a blast crisis of CML lacking one of the chromosome 7 pair (15). Loss of chromosome Y occurs in 8% of chronic phase CML patients and may merely reflect a nonspecific change associated with aging (16). As stage IV (remission phase) chromosomal abnormalities, only Ph^1 translocation and small clones with an abnormal chromosome in addition to the Ph^1 translocation are known. Based on the findings of the present study, the incidence of the appearance of clones which have abnormal chromosomes in addition to the Ph^1 chromosome is highest in blastic phase, intermediate in the early stage of blastic phase (stage II) and lowest in chronic phase. Chromosomal analysis alone is not the best marker for diagnosing the onset of blastic phase; however, it is a useful parameter when used combination with clinical and hematological results.

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REFERENCES

1. Kitazima, K. and Kimura, I.: Blastic crisis. In *Chronic Myelocytic Leukemia*, Niigata symposium. ed. H. Uchino and A. Shibata, Ishiyaku publication, Tokyo, pp. 144-151, 1979 (in Japanese).
2. Casperson, T., Zech, L. and Johansson, C.: Differential binding of alkylating flurochromes in human chromosomes. *Exp. Cell Res.* **60**, 315-319, 1970.
3. Seabright, M.: A rapid banding technique for human chromosomes. *Lancet* **ii**, 971-972, 1971.
4. Sumner, A. T.: A simple technique for demonstrating centromeric heterochromatin. *Exp. Cell Res.* **75**, 304-306, 1972.
5. Sehested, J.: A simple method for R banding of human chromosomes, showing a pH-dependent connection between R and G bands. *Humangenetik* **21**, 55-58, 1974.
6. Paris Conference (1971).: *Standardization in Human Geneties. Birth Defects*: Original article series. The national foundation, New York. Vol. VIII, No. 7, 1972.
7. Sandberg, A. A.: Chromosomes in the chronic phase of CML. *Virchows Arch. B Cell Pathol.* **29**, 51-55, 1978.
8. Sonta, S-I. and Sandberg, A. A.: Chromosomes and causion of human cancer and leukemia XXIX. Further studies on karyotypic progression in CML. *Cancer* **41**, 153-163, 1978.
9. Rowley, J. D.: Chromosome abnormalities in the Acute phase of CML. *Virchows Arch. B Cell Pathol.* **29**, 57-63, 1978.

10. Mintz, U., Vardiman, J., Golomb, H. M. and Rowley, J. D.: Evolution of karyotypes in Philadelphia (Ph^1) chromosome-negative chronic myelogenous leukemia. *Cancer* **43**, 411-416, 1979.
11. Rowley, J. D.: Mapping of human chromosomal regions related to neophasia : Evidence from chromosomes 1 and 17. *Proc. Natl. Acad. Sci. USA* **74**, 5729-5733, 1977.
12. Gahrton, G., Friberg, K., Zech, L. and Lindstein, J.: Duplication of part of chromosome No. 1 in myeloproliferative disease. *Lancet* ', 96-97, 1978.
13. Slater, R. M., Philip, P., Badserg, E., Behrendt, H., Hansen, N. E. and Van Heerde, P.: A 14q+ chromosome in a B-cell acute lymphocytic leukemia and in a leukemic non-endemic Burkitt lymphoma. *Int. J. Cancer* **23**, 639-649, 1979.
14. Miyamoto, K., Miyano, K., Miyoshi, I., Hamasaki, K., Nishihara, R., Terao, S., Kimura, I., Maeda, K., Matsumura, K., Nishijima, K. and Tanaka, T.: Chromosome 14q+ in a Japanese patient with Burkitt's lymphoma. *Acta Med. Okayama* **34**, 61-65, 1980.
15. Como, R. M. and Graze, P. R.: Emergence of a cell line with extreme hypodiploidy in blastic crisis of chronic myelocytic leukeima. *Blood* **53**, 707-711, 1979.
16. Lawler, S. D.: The cytogenetic of chronic granulocytic leukemia. *Clin Hematol* **6**, 55-75, 1977.