Chromosomes and Causation of Human Cancer and Leukemia. XXIV. Unusual and Complex Ph[1] Translocations and Their Clinical Significance

By Shin-ichi Sonta and Avery A. Sandberg

An evaluation is presented of the clinical, hematologic, and survival picture in 30 known cases of chronic myelocytic leukemia (CML) with unusual or complex Ph[1] translocations. An "unusual" Ph[1] translocation differs from the standard one in that the deleted part of chromosome 22 is translocated onto chromosomes or chromosomal areas other than the long arm of chromosome 9; a "complex" Ph[1] translocation indicates a rearrangement involving three or more chromosomes but invariably including No. 22, usually No. 9, and at least one other chromosome. This study included two cases with unusual and four with complex Ph[1] translocations from our laboratory. The information on the remaining 24 cases was obtained through a questionnaire submitted to the various investigators. Even though the number of patients with unusual or complex Ph[1] translocations available for analysis is still relatively small (in all probability the number does not exceed 10% of all Ph[1] positive CML cases observed), the data collected on the 30 patients indicate that the clinical, prognostic, and hematologic features of these cases are not significantly different from those of CML cases with the standard type of Ph[1] translocation. Except for the long arms of chromosomes 9 and 22, no other chromosome appeared to be involved more often than others in unusual and complex translocations. It would appear that the crucial event in CML is the genesis of the Ph[1] chromosome from chromosome 22 and that the site and complexity of the translocation of the deleted part of the No. 22 may be of only minor significance in determining the course of the disease.

THE MAJORITY OF CASES of chronic myelocytic leukemia (CML) are characterized by the presence of a Ph[1] chromosome in the bone marrow and blood cells; about 15% of CML cases are Ph[1]-negative.[1-3] The prognosis and survival of the latter group are much worse than those for the Ph[1]-positive group. Most cases of CML are associated with a Ph[1] chromosome due to a translocation between chromosomes 9 and 22, i.e., t(9;22)(q34;q11),[4] which will be referred to as the "standard" Ph[1] translocation. However, unusual and complex Ph[1] translocations have been described in a small number (probably no more than 10%) of the patients with CML.

In the study to be presented an "unusual" (simple) translocation is one in which the deleted part of chromosome 22 is translocated onto chromosomes or chromosomal areas other than the long arm of chromosome 9. In the "complex" Ph[1] translocation a rearrangement involving at least three chromosomes, but invariably No. 22 and usually No. 9, takes place. In compiling the data on

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Address for reprint requests: Avery A. Sandberg, M.D., Roswell Park Memorial Institute, 666 Elm Street, Buffalo, N. Y. 14263.

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unusual and complex cases of Ph[1]-positive CML, only those in which a morphologically characteristic Ph[1] chromosome was present were included in the analysis. The purpose of the present study was to ascertain whether patients with CML and unusual or complex Ph[1] translocations have a different clinical, hematologic, and survival picture than the great majority of the CML patients with the standard type of Ph[1] translocation.

MATERIALS AND METHODS

Since no one laboratory has been able to collect a sufficient number of cases with unusual or complex Ph[1] translocations for analysis, the data to be presented were obtained by sending out questionnaires to all the authors of reports of cases with such translocations, in addition to the data on cases observed at our institution or transmitted to us personally. The results to be presented are based on information supplied by these authors, to whom we are very grateful for their cooperation.

As part of our continuing studies of the chromosomes in leukemia, 39 cases of Ph[1]-positive CML were examined with banding techniques during the period between February 1975 and October 1976. Of the 39 patients, 25 had a Ph[1] with evidence of translocation, 1 had a Ph[1] without evidence of translocation,[5] and 13 had karyotypic changes in addition to the Ph[1]. Of the 25 patients with only a Ph[1] translocation, 24 had the standard type of translocation between chromosomes 22 and 9, and 1 had a complex Ph[1] translocation between chromosomes 22, 17, and 9. In addition, we have followed 19 cases with Ph[1]-positive CML described by us previous to 1975,[6] observed between March 1973 and February 1975. Two of these 19 cases had unusual translocations and 3 had complex ones.

To the best of our knowledge 14 cases with unusual (simple) and 16 with complex Ph[1] translocations have been observed, i.e., described in the literature to date or communicated to us personally (Table 1); these cases include 2 unusual and 4 complex Ph[1] translocations observed by us.

RESULTS

The 30 cases of CML with Ph[1]-translocations other than the standard one are shown in Table 1. All of the cases had a morphologically typical Ph[1] chromosome originating from chromosome 22, except for case 116, whose Ph[1] was very small. The chromosomes participating in the 14 cases with unusual (simple) Ph[1] translocations were Nos. 2 (2 cases), 6, 9 (short arm), 11 (2 cases), 13, 14, 16, 17, 19 (2 cases), 21, and 22. The chromosomes involved in the 16 cases with complex translocations were Nos. 3, 4, 5, 6 (2 cases), 7 (2 cases), 8, 9 (14 cases), 10 (2 cases), 11 (2 cases), 13 (2 cases), 14, 15 (2 cases), 17, 19, 21, and 22. The participation of chromosome 9 in 14 of the 16 complex translocations is particularly worthy of note. In the total group of 30 cases with unusual or complex Ph[1] translocations, chromosome 9 was involved in 15 cases, No. 11 in 4 cases, and No. 6 and 13 in 3 cases each. When chromosome 9 was involved in a complex translocation the break was usually at band q34, the usual location of the break in the standard type of Ph[1] translocation. In 11 complex Ph[1] translocations 3 chromosomes were involved, i.e., chromosomes 9, 22, and a third one. In three other cases (patients 108, 110, and 113) involvement of 4–5 chromosomes and in two cases (104, 116) still more complicated Ph[1] translocations were present.

In no case did the sex chromosomes participate in a Ph[1] translocation. In one instance (patient 8) a missing Y chromosome developed during the course of the disease. Such a karyotypic finding is not unusual in CML and, in fact, may occur in elderly males without any disease.[7,8] To date, chromosomes 1, 8, 18, and 20 have not been reported to be involved in a Ph[1] translocation.

Table 1. Simple and Complex Ph[1] Translocations Involving Chromosome 22 and Those Listed in the Table

Case No.	Chromosome Involved	Type of Translocation	Reference
Unusual (simple) translocation			
1	2	t(2;22)(q37;q11or12)	Hayata et al., 1973[6,11]
2	2	t(2q+;22q−)	Van Den Berghe et al. (personal communication)
3	6	t(6;22)(p25;q12)	Mammon et al., 1976[12]
4	9	t(9p+q+;11p−;22q−)	Gahrton and Friberg (personal communication)
5	11	t(11;22)(p15;q11?)	Muldal et al., 1975[13]
6	11	t(11p+;22q−)	Engel et al. (personal communication)
7	13	t(13;22)(p13;q11or12)	Hayata et al., 1975[6]
8	14	t(14;22)(q23;q11?)	Ishihara et al. (personal communication)
9	16	t(16p+;22q−)	Engel et al., 1975[14,15]
10	17	t(17;22)(q25;q11)	Matsunaga et al., 1976[16]
11	19	t(19q+;22q−)	Gahrton et al., 1974[17]
12	19	t(19;22)(q13;q11)	Lawler et al., 1976[18]
13	21	t(21q+;22q−)	Bottura et al., 1974[19]
14	22	t(22;22)(q13;q12)	Foerster et al., 1974[20]
Complex translocation			
101	3, 9	t(3;9;22)(p14or21;q34;q?)	Nowell et al., 1975[21]
102	4	ins(4;22)(q31;q?)*	Horland et al., 1976[22]
103	5, 9	t(5;9;22)(q12;q34;q?)	Nowell et al., 1975[21]
104	9	abnormal 9q+;22q−	Hayata et al., 1975[6]
105, 106	6, 9 (2 cases)	t(6;9;22)(p21;q34;q11)	Potter et al., 1975[23]
107	7, 9	t(7;9;22)	Nowell (personal communication)
108	7, 9, 11	t(7;9;11;22)	Ishihara et al. (personal communication)
109	9, 10	t(9;10;22)(q34;q11;q11or12)	Hayata et al., 1975[6]
110	9, 10, 15, 19	t(9q+;10p+q−;15q−;19q+;22q−) (q34;p15q22;q22;q12;q12)	Hayata and Sasaki, 1976[24]
111	9, 11	t(9;22;11)(q34;q11;q13)	Lawler et al., 1976[18]
112	9, 13	9q−q+,ins(13;9),22q−†	Hayata et al., 1975[6]
113	9,13,15	t(9q+;13q−q+;15q−;22q−) (q34;q12;q22;q11)	Potter et al., 1975[23]
114	9, 14	t(9;14;22)(q34;q24;q11)	Potter et al., 1975[23]
115	9, 17	t(9;17;22)(q34;q21;q11)	Sonta and Sandberg, 1977[26]
116	21, 22	t(21p+;22p+;22q−)	Ishihara et al., 1974[25]

*Now thought to be t(4;9;22)(q23;q34;q11) [Wolman, personal communication, and Rowley et al.[28]].

††(9; 13; 22) (9pter→9q21::22q11or12; 13pter→13q13::9q21→9q34::13q13→13qter; 22pter →22q11or12::?).

Some of the clinical features of the 30 patients with unusual or complex Ph[1] translocations and their survival (the latter compared with that of Ph[1]-negative patients with CML and those with a standard Ph[1] translocation) are shown in Table 2 and Fig. 1, respectively. In 19 patients in whom chromosomal analysis was performed on more than one occasion, 6 showed further chromosomal changes: 5 in the blastic phase and 1 during remission of the disease. The 13 remaining cases have so far shown no further karyotypic abnormalities. The additional chromosomal changes observed in the 6 cases (all males) are shown in Table 3.

Table 2. Summarized Information on the Patients With Unusual (Simple) and Complex Ph[1] Translocations

Case No.	Survival (mo)	Present Status	Further Chromosomal Changes	Splenomegaly	Other Unusual Features
Unusual (simple) translocation					
1	9	Dead	No	Yes	Hepatomegaly
2	13	Remission	No	Yes	
3	24	Remission	No	No	Neutrophilic leukocytosis
4	11	Remission	No	Yes	
5	?	Blastic phase?	—	Yes	
6	11	Remission	—	No	
7	58	Blastic phase	No	Yes	
8	19	Remission	Yes	No	Gynecomastia and pleural effusion
9	31	Blastic phase	—	Yes	Hemothorax
10	84	Remission	No	Yes	
11	36	Dead	—	Yes	
12	?	Remission	—	Yes	
13	105	Remission	No	No	Hepatomegaly
14	18	Dead	—	—	
Complex translocation					
101	6	Dead	—	Yes	
102	16	Remission	—	Yes	Pernicious anemia
103	12	Dead	Yes	No	Sickle cell anemia
104	57	Dead	No	Yes	Septicemia
105	21	Dead	Yes	Yes	
106	16	Dead	Yes	No	
107	10	Remission	No	No	
108	31	Blastic phase	Yes	No	Thrombocytosis after treatment
109	32	Blastic phase	No	Yes	
110	14	Remission	—	Yes	
111	18	Dead	Yes	—	
112	90	Dead	No	No	
113	21	Remission	No	No	
114	22	Remission	No	No	
115	5	Remission	No	Yes	
116	3	Remission	No	No	

An evaluation of some of the clinical features of these cases revealed that splenomegaly was present in 15. Examination of the blood revealed a mean white blood cell count of 158,000/cu mm, a platelet count of 323,000/cu mm, a hematocrit of 36.3%, and a hemoglobin of 11.2 g/dl (Table 4). The mean differential of the blood leukocytes of the patients with simple or complex translocations is shown in Table 4. The rather high percentage of myeloblasts shown in the column for the unusual translocations is affected by the presence in this group of one patient in the blastic phase (>80% myeloblasts) of CML at the time of diagnosis. When this case is excluded, the percentage of myeloblasts in the peripheral blood is very similar in both groups.

DISCUSSION

Even though the number of patients with unusual and complex Ph[1] translocations available for analysis is still relatively small, it would appear that, except

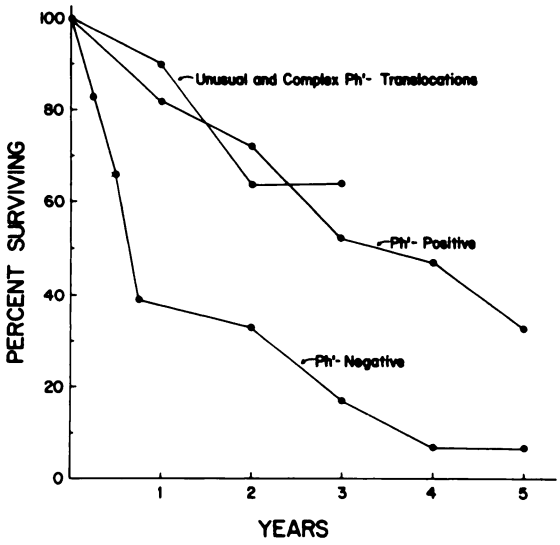

Fig. 1. Survival of Ph[1]-positive and Ph[1]-negative CML patients based on data of Ezdinli et al.[2] Survival of patients with unusual (simple) or complex Ph[1] translocations is shown for initial 3 yr after diagnosis, since an insufficient number had been diagnosed 5 yr ago (see text for discussion).

Table 3. Further Changes in the Chromosomal Pictures of the Patients Studied

Case No.	Status	Initial Karyotypes*	Further Changes*
Unusual (simple) translocation			
8	Remission	46,XY,Ph[1],t	→46,XY,Ph[1],t/45,X,Ph[1],t
Complex translocation			
103	Blastic phase → dead	47,XY,Ph[1],t,+Ph	→48,XY,Ph[1],t,+Ph[1],+8
105	Blastic phase → dead	46,XY,Ph[1],t	→50,XY,Ph[1],t,+8,+15,+17,+Ph[1]
106	Blastic phase → dead	46,XY,Ph[1],t	→46,XY,Ph[1],t/46,XY,Ph[1],t,1q+
108	Blastic phase	45,XY,Ph[1],t,−9	→45,XY,Ph[1],t,−9/46,XY,Ph[1]/(standard) 47,XY,Ph[1],+Ph[1] (standard +Ph[1])
111	Blastic phase → dead	46,XY,Ph[1],t	→variant clones

*t indicates either unusual (simple) or complex Ph[1] translocations.

Table 4. Peripheral Blood Findings Before Treatment in 20 Patients With Unusual (Simple) and Complex Translocations

	Unusual (Simple)	Complex	Total
WBC (× 10^3/cu mm)	183	142	158
Platelets (× 10^3/cu mm)	328	313.9	322.8
Hct (%)	35.5	36.6	36.3
Hb (g/dl)	12.4	10.7	11.2
Differential (%)			
Myeloblasts	14.2*	7.6	10.0*
Promyelocytes	5.1	2.6	3.5
Myelocytes	10.6	13.1	12.2
Metamyelocytes	8.1	8.9	8.6
Lymphocytes	3.6	8.3	6.6
Monocytes	1.4	1.5	1.5
Eosinophils	2.7	2.1	2.3
Basophils	3.6	2.7	3.0
Neutrophils	48.2	49.6	49.1

*Including one case in the blastic phase at the initial diagnosis.

for the distal end of the long arm of chromosome 9, no other chromosome participated in such translocations with unusual frequency. Further chromosomal changes were observed in 6 of the 19 cases studied repeatedly; 5 of these were in the blastic phase of CML. In the other case further karyotypic abnormalities apparently developed during remission. The frequency of cases with additional abnormalities and the types of such abnormalities were similar to those seen in the blastic phase of the patients with the standard type of Ph^1 translocation.[2,6-8]

The mean age (45 yr), the clinical data, and the laboratory findings of the CML patients with unusual and complex translocations were not significantly different from those of patients with Ph^1-positive CML with the standard type of translocation.[2,6-8] As shown in Fig. 1, the survival of the patients with unusual or complex Ph^1 translocations during the initial 3 yr after diagnosis was comparable to that of the other Ph^1-positive cases, and the 5 yr survival could predictably be assumed to be as good; both Ph^1-positive groups had a much better survival than the Ph^1-negative group with CML (Fig. 1).

Since the introduction of banding techniques and the establishment of the nature of the Ph^1 chromosome and its translocation are rather recent,[4] the number of patients with unusual and complex Ph^1 translocations who have survived more than 4–5 yr is still too small to be expressed confidently in Fig. 1, but it would appear that such survival (i.e., 5 yr or more) will be at least comparable to that of the other Ph^1-positive cases. Though not shown in Fig. 1, an analysis revealed that there was no significant difference in the survival of the cases with simple Ph^1-translocations versus that of the complex ones. Thus, the mean length from the blastic crisis to death in the unusual cases was 6.5 mo, a period very similar to that described previously by Ezdinli et al.[2]

It would appear that the presence of the Ph^1 chromosome is of more importance in determining the clinical and survival features of CML, rather than the nature of the chromosomes involved and/or the complexity of such translocations, i.e., whether the genesis of the Ph^1 is due to the standard type of translocation or to unusual or complex ones.

On the assumption that morphologic modification of the Ph^1 may introduce an important and complicating factor affecting some of the parameters evaluated by us, we have not included some cases of CML with interesting Ph^1 translocations in which the morphologic features of the Ph^1 did not meet the usual criteria for such an abnormal chromosome.[9,10,14,27]

Only through an accumulation in the future of a large series of patients with unusual or complex Ph^1 translocations and a comparison of their survival with that of CML patients with the standard Ph^1 translocation will the significance of the unusual and complex translocations become more firmly established.

REFERENCES

1. Sandberg AA, Hossfeld DK: Chromosomal changes in human tumors and leukemias, in: Handbuch der Allgemeinen Pathologie, vol 6. Berlin, Springer, 1974, pp 141–287

2. Ezdinli EZ, Sokal JE, Crosswhite LH, Sandberg AA: Philadelphia-chromosome-positive and -negative chronic myelocytic leukemia. Ann Intern Med 72:175–182, 1970

3. Canellos GP, Whang-Peng J, DeVita VT: Chronic granulocytic leukemia without the Philadelphia chromosome. Am J Clin Pathol 65:467–470, 1976

4. Rowley JD: A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. Nature 43:290–293, 1973

5. Sonta SI, Oshimura M, Sandberg AA: Chromosomes and causation of human cancer and leukemia. XXI. Cytogenetically unusual cases of leukemia. Blood 48:697-705, 1976

6. Hayata I, Sakurai M, Kakati S, Sandberg AA: Chromosomes and causation of human cancer and leukemia. XVI. Banding studies of chronic myelocytic leukemia, including five unusual Ph[1]-translocations. Cancer 36:1177-1191, 1975

7. Sakurai M, Hayata I, Sandberg AA: Chromosomes and causation of human cancer and leukemia. XV. Prognostic value of chromosomal findings in Ph[1]-positive CML. Cancer Res 36:313-318, 1976

8. Sakurai M, Sandberg AA: The chromosomes and causation of human cancer and leukemia. XVIII. The missing Y in AML and Ph[1]-positive CML. Cancer 38:762-769, 1976

9. Pravtcheva D, Andreeva P, Tsaneva R: A new translocation in chronic myelogenous leukemia. Hum Genet 32:229-232, 1976

10. Engel E, McGee BJ, Flexner JM, Russell MT, Myers BJ: Philadelphia chromosome (Ph[1]) translocation in an apparently Ph[1] negative, minus G22, case of chronic myeloid leukemia. N Engl J Med 291:154, 1974

11. Hayata I, Kakati S, Sandberg AA: A new translocation related to the Philadelphia chromosome. Lancet 2:1385, 1973

12. Mammon Z, Grinblat J, Joshua H: Philadelphia chromosome with t(6;22)(p25;q12). N Engl J Med 294:827-828, 1976

13. Muldal S, Mir MA, Freeman CB, Geary CG: A new translocation associated with the Ph[1] chromosome and an acute course of chronic granulocytic leukaemia. Br J Cancer 31:364-368, 1975

14. Engel E, McGee BJ, Flexner JM, Krantz SB: Translocation of the Philadelphia chromosome onto the 17 short arm in chronic myeloid leukemia: A second example. N Engl J Med 293:666-667, 1975

15. Engel E, McGee BJ, Flexner JM, Krantz SB: Chromosome band analysis in 19 cases of chronic myeloid leukemia: 9 chronic, 10 blastic, two with Ph[1] (22q-) translocation on 17 short arm. Ann Genet 18:239-240, 1975

16. Matsunaga M, Sadamori N, Tomonaga Y, Tagawa M, Ichimaru M: Chronic myelogenous leukemia with an unusual karyotype: 46,XY,t(17q+;22q-). N Engl J Med 295:1537, 1976

17. Gahrton G, Zech L, Lindsten J: A new variant translocation (19q+, 22q-) in chronic myelocytic leukemia. Exp Cell Res 86:214-216, 1974

18. Lawler SD, O'Malley F, Lobb DS: Chromosome banding studies in Philadelphia chromosome positive myeloid leukaemia. Scand J Haematol 17:17-28, 1976

19. Bottura C, Coutinho V: G1G translocation and chronic myelocytic leukaemia. Blut 29:216-218, 1974

20. Foerster W, Medau HJ, Löffler H: Chronisch myeloische Leukämie mit Philadelphia-Chromosom und Tandemtranslokation am 2 Chromosom N., 22;46,XX,tan(22q+;-22q-). Klin Wochenschr 52:123-126, 1974

21. Nowell PC, Jensen J, Gardner F: Two complex translocations in chronic granulocytic leukemia involving chromosomes 22, 9 and a third chromosome. Humangenetik 30: 13-21, 1975

22. Horland AA, Wolman SR, Distenfeld A, Cohen T: Another variant translocation in chronic myelogenous leukemia. N Engl J Med 294:164-165, 1976

23. Potter AM, Sharp JC, Brown MJ, Sokol RJ: Structural rearrangements associated with the Ph[1] chromosome in chronic granulocytic leukaemia. Humangenetik 29:223-228, 1975

24. Hayata I, Sasaki M: A case of Ph[1]-positive chronic myelocytic leukemia associated with complex translocations. Proc Jpn Acad 52:29-32, 1976

25. Ishihara T, Kohno S-I, Kumatori T: Ph[1]-translocation involving chromosome 21 and 22. Br J Cancer 29:340-342, 1974

26. Sonta S, Sandberg AA: A new complex Ph[1]-translocation involving 3 chromosomes. J Natl Cancer Inst (in press)

27. Lawler SD, Lobb DS, Wiltshaw E: Philadelphia-chromosome positive bone-marrow cells showing loss of the Y in males with chronic myeloid leukaemia. Br J Haematol 27:247-252, 1974

28. Rowley JD, Wolman SR, Horland AA: Another variant translocation in chronic myelogenous leukemia—revisited. N Engl J Med 295: 900-901, 1976