Chronic Myelogenous Leukemia with t(9;22) and t(8;11): A New Chromosome Anomaly

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ABSTRACT: *A case of chronic myelogenous leukemia in an elderly man with a new translocation, t(8;11)(q24;q13), associated with a Philadelphia t(9;22) translocation is described. The clinical and hematologic aspects of the disease did not seem to differ from those of the usual cases of chronic myelogenous leukemia except for a basophilic blast crisis.*

INTRODUCTION

A t(9;22)(q34;q11) translocation (Philadelphia chromosome), found in 92%–95% of cases with chronic myelogenous leukemia (CML), is sometimes associated with other structural chromosome anomalies [1]. Chromosome #8, however, particularly the q24 region, is very seldom involved [2–4]. We report herein a case of CML in an elderly patient where both t(9;22) and t(8;11)(q24;q13) were found.

CASE REPORT

Patient D. A., an 86-year-old man born in the north of France and with no previous medical history, entered hospital in July 1983 because of hyperleukocytosis found on a systematic blood count. This man had three healthy children. There were no general symptoms or bleeding, and no organomegaly was found.

Blood findings showed slight anemia (hemoglobin 11.5 g/dl), hyperleukocytosis (WBC 78.10^9/L), and a platelet count of 180 $\times$ 10^9/L. The differential count showed 44% neutrophils, 3% basophils, 27% immature granulocytes (mostly myelocytes and metamyelocytes), but no circulating blasts. The bone marrow was hypercellular and showed an increase in granulocytes with 10% blasts, myeloblasts, and promyelocytes. The leukocyte alkaline phosphate score was reduced to 5; (normal, 20–80). Other findings were normal, except for a moderate hyperuricemia.

Treatment consisted of busulfan (4 mg/day); and a normalization of the blood count was obtained within 1 month. In July 1984, the hemoglobin dropped to 10 g/dl and platelets to 100 $\times$ 10^9/L. There were 29 $\times$ 10^9/L leukocytes with 49% neutrophils, 11% basophils, 10% immature granulocytes; blasts and myeloblasts accounted for 10% of the differential count. The myelogram confirmed the diagnosis

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of blast crisis showing 22% blasts belonging to the granulocytic series. Subsequent blood counts showed an increase in basophilia (reaching 30% of the differential count) but with a stable blast percentage. In July 1985, 24 months after the diagnosis of CML and 12 months after that of blast crisis, the patient is still alive.

METHODS AND RESULTS

Cytogenetic studies were performed on blood after 48-hour culture without stimulation by mitogens. Stimulation of lymphocytes by PHA was a failure: all photographed cells showed the Ph chromosome (the patient was then already in blast crisis). RHG- and GTG-banding were performed by heating and trypsin technique.

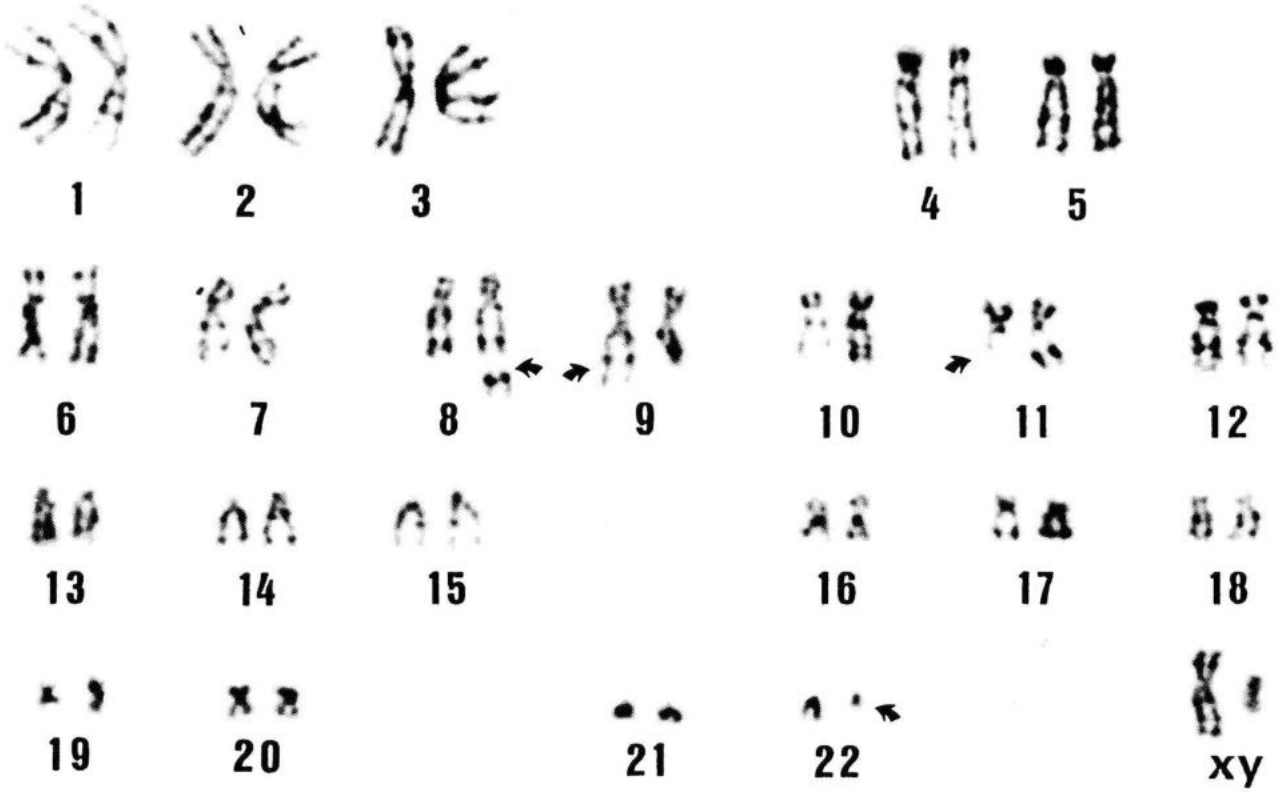
Chronic Phase

The studies performed in July 1983 (21 metaphases) and February 1984 (22 metaphases) showed both t(9;22) and t(8;11)(q24;q13) in all cells examined (Fig. 1).

Blast Crisis

Hematologic signs of imminent blast crisis occurred in July 1984. This was confirmed by cytogenetic studies, which showed at that time several abnormal clones: 46,XY,t(9;22),t(8;11) (four mitoses); 46,XY,t(9;22),t(8;11),r15,del(6)(p21→pter) (18 mitoses); 46,XY,t(9;22),t(8;11),t(6;12)(q21;q24) (two mitoses). Finally, in December 1984, a karyotype showed only one cellular clone (eight cells examined): 46,XY,t(9;22),t(8;11),r15,del(6)(p21→pter) (Fig. 2).

Figure 1 CML in chronic phase. Karyotype with t(9;22) and t(8;11). GTG-banding.



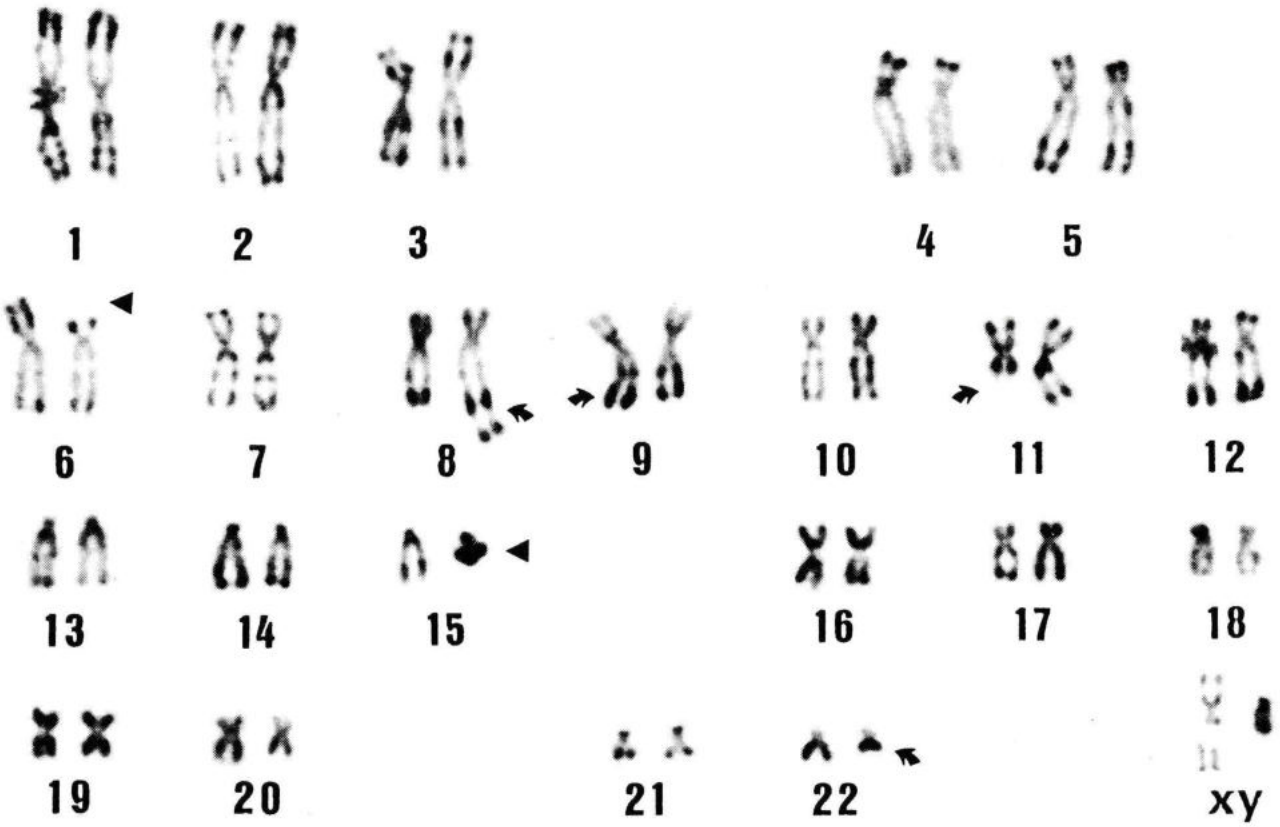


Figure 2 CML in blastic phase. Karyotype with t(9;22),t(8;11), r15 and del(6)(p21→pter). RHG-banding.

DISCUSSION

We report herein an elderly patient with CML, the coexistence of two balanced structural chromosome changes: t(9;22)(q34;q11), a usual translocation found in about 90% of CML [5], and an unusual translocation between chromosome #8 and #11, involving 8q24 and 11q13. Structural changes in the 8q24 band [t(8;14) and its variants] are constant findings in Burkitt's lymphoma or Burkitt's-type ALL [6]. To our knowledge structural changes involving 8q24 region have been described in CML only in t(8;22)(q24;q11) [2–4], and our case is the first report of t(8;11)(q24;q13) in this blood disorder.

Chromosome #11 anomalies have been found in acute monocytic leukemias (M5, FAB) [7], and usually involve 11q23 band and less often 11q13 or 14 [8]. Several cases of t(11;14)(q13;q32) also have been reported in chronic lymphocytic leukemia (CLL) [9].

Complex translocations involving three chromosomes: t(9;11;22)(q34;q13;q11) [4, 10–12]; t(11;14;22)(q13;q32;q11) [13, 14]; or even four chromosomes: t(6;9;11;22)(q21;q34;q13;q11) [15] have already been seen in CML. In those cases, as in our patient, the exchange on chromosome #11 affects the 11q13 region, which also corresponds to a fragile site [16]. Therefore, it seems probable that in CML preferential exchange zones exist which can be involved in several malignant blood disorders (i.e., 8q24 band in Burkitt's lymphoma or B-ALL; 11q13 in CLL). Molecular studies have placed the c-*abl* oncogene on the long arm of chromosome #9 at the q34 region [17].

In CML with a t(9;22) Ph chromosome, this oncogene is transferred to chromosome #22 at 22q11 [18], thus, fusing the c-*abl* oncogene with the *bcr* gene, and resulting in the transcription of a chimeric mRNA [19]. In the present report, how-

ever, the chromosome anomalies also included the involvement of the 8q24 region, which contains the cellular oncogene c-*myc* [20], in another chromosomal rearrangement, without particular clinical or hematologic features except for an important basophilia. It is well recognized that in Burkitt's lymphoma and ALL, with translocations between 8q24 and chromosomes #2, #14, or #22, c-*myc* has been found to be translocated to one of these chromosomes in Burkitt's cell lines [20] and fresh cells [21].

In our case, studies of the DNA by Southern blotting analysis after digestion with several restriction enzymes failed to show any rearrangement of c-*myc* when using a probe corresponding to total third exon of c-*myc* (data not shown). The breakpoint, therefore, seems different from that found in Burkitt's lymphoma or ALL.

We could not study the *bcl*-1 region situated on chromosome 11q13. This region corresponds to the breakpoint of t(11;14), which is found in some B lymphomas and leukemias [22]. This rearrangement, therefore, cannot be excluded in the present case.

In our patient, 8q24, 9q34, and 11q13 regions, corresponding respectively to c-*myc* and c-*abl* oncogenes, and *bcl*-1 regions, were involved in structural rearrangements in the hematopoietic stem cells.

Finally, this patient could be studied both in the chronic phase and blast crisis of CML. The chromosome anomalies reported (ring chromosome #15, 6p deletion) are different from those frequently observed in the literature [trisomy 8, 19, double Ph, loss of Y, iso(17q)] [23]. Our case seems to indicate that t(8;11), which coexists with the usual t(9;22), may announce the blast phase that occurred only 1 year after the diagnosis of CML.

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