CONCISE REPORT

Common ALL With Pre-B-Cell Features Showing (8;14) and (14;18) Chromosome Translocations

By G. J. Mufti, T. J. Hamblin, D. G. Oscier, and Sharron Johnson

A 21-yr-old man presented with inguinal lymphadenopathy and splenomegaly. The peripheral blood showed a high blast cell count. The morphological and immunological features of the blast cells were consistent with the diagnosis of common acute lymphoblastic leukemia (ALL) with 15% pre-B-cells. Banded karyotype analysis of the bone marrow cells, using the technique of methotrexate synchronization, revealed the presence of (8;14) and (14;18) chromosome translocations, a finding that has not been previously documented. The significance of these findings is discussed.

RECENT ADVANCES in immunology have led to important insights into leukocyte differentiation and the cellular origin of human leukemias. Four major subtypes of acute lymphoblastic leukemia (ALL) are now well recognized; common ALL (cALL), B-ALL, T-ALL, and unclassified or null ALL. It has recently been documented that, in 20%-30% of all cALL cases, blasts of pre-B-cell phenotype, containing variable amounts of intracytoplasmic mu chains but no surface immunoglobulins, are present. Furthermore, the majority of cases of cALL that have been studied using genetic probes have shown rearrangements of immunoglobulin genes, and thus appear to be genetically committed to B-cell differentiation even when detectable immunoglobulin is lacking. These findings are supported by in vitro differentiation of cALL cells to B cells. In conjunction with the immunologic cell marker studies, improvements in cytogenetic techniques have provided new evidence of a close correlation between particular chromosomal and specific immunologic phenotypes in malignant lymphomas. For example, cases reported as B-cell ALL (FAB L3) have a translocation involving chromosomes nos. 8 and 14, accompanied by a predominant pre-B-cell phenotype. In addition, Yunis et al. have recently described a (14;18) translocation in lymph node cells from 16 of 19 patients with follicular lymphomas. Furthermore, (8;14) was detected in 3 of 3 cases of small non-cleaved-cell (non-Burkitt's) lymphoma and 2 of 3 large cell immunoblastic lymphomas. In this report, we document a patient with cALL (FAB L2) with some cells showing pre-B-cell phenotype. Cytogenetic analysis of his blast cells showed a translocation between a chromosome no. 8 and a chromosome no. 14, accompanied by a translocation between the homologous chromosome no. 14 and a no. 18. We discuss the probable implications of these findings.

CASE REPORT

A 21-year-old male printer presented in February 1982 with a 4-mo history of tiredness, painful lumps in the left groin, and a swelling below the left knee of 6-wk duration. On examination, the glands in the left inguinal region were enlarged, tender, and measured 8 cm x 5 cm. There was no lymphadenopathy elsewhere. There was a firm, nontender swelling 5 cm x 3 cm arising from the upper third of the left tibia. Examination of the abdomen revealed 5-cm tender splenomegaly and 2-cm hepatomegaly.

Investigations showed WBC 92.1 x 10^9/liter (blasts 91%, neutrophils 6%, lymphocytes 2%, monocytes 1%); Hb 14.9 g/dl, platelets 59 x 10^9/liter, bilirubin 15 umole/liter (normal <14), alkaline phosphatase 294 lU/liter (normal 30-95), aspartate transaminase (AST) 114 IU/liter (normal <14), lactate dehydrogenase (LDH) 1,085 IU/liter (normal 30-95), and serum urate 0.60 mmole/liter (normal 0.22-0.38). X-rays of the abdomen confirmed splenomegaly and chest x-rays, including the mediastinal views, were within normal limits. X-rays of the left knee and 99mTc bone scan were within normal limits. Bone marrow aspirate and biopsy were densely hypercellular, almost entirely replacing the normal marrow. A population of large blast cells with prominent nuclei were present, along with small blasts with a high nucleo-cytoplasmic ratio. Nuclear and cytoplasmic vacuolation was absent in blast cells (Fig. 1). The leukemic cells were negative for acid phosphatase, periodic acid-Schiff (PAS), Sudan black, and chloroacetate esterase stains. A diagnosis of FAB L2 ALL was made.

MATERIALS AND METHODS

For immunologic and biochemical analysis, heparinized marrow and peripheral blood samples were collected in RPMI medium. Mononuclear cells were separated on Ficoll-Isopaque, washed, and tested for expression of surface membrane leukemia-associated antigens by indirect immunofluorescence, using previously described methods. Antiserum used included anti-acute lymphoblastic leukemia serum, anti-J5, anti-human Ia-like serum, and anti-human T-lymphoid antiserum. Cells were also examined by direct immunofluorescence for surface membrane immunoglobulin using goat anti-human Ig. For terminal deoxynucleotidyl transferase (TdT) staining, cells were pelleted onto glass slides in a cytocentrifuge.
**Clinical Course**

Figure 2 summarizes the patient's clinical course and the chemotherapy he received. Five weeks after starting the chemotherapy, the inguinal lymphadenopathy and the swelling on the upper third of the tibia partially regressed, but the splenomegaly persisted. The bone marrow and peripheral blood smears continued to show blast cells. Despite intensive chemotherapy, he died of resistant leukemia and septicemia 14 wk after presentation.

**DISCUSSION**

Most of the blast cells in this patient expressed the cALL antigen and had a high level of terminal deoxynucleotidyl transferase activity, thus confirming the diagnosis of common ALL. In addition, 15% of the blast cells contained cytoplasmic mu chains. This phenotype is consistent with the differentiation of some of the blast cells to pre-B-cells.

Cytogenetic analysis of this patient's peripheral blood is of particular interest. The results are indicated in Table 1. All the cells showing chromosomal abnormalities were found to have a t(8;14)(q23;q32) and t(14;18)(q32;q21). The t(8;14) abnormality is consistently noted in patients with B-cell ALL (FAB L3) and has recently been documented in lymph node cells from cases with small non-cleaved-cell (non-Burkitt's) lymphomas and large cell immunoblastic lymphomas. The t(8;14)(q24;q32) has been reported in the blast cells of one case of common ALL with pre-B-cell features. Although the immunologic phenotype of this patient was that of cALL, the morphological features were those of FAB L3 ALL. The 14q+ marker has been detected in the majority of these cases, and the t(14;18) has been observed in some cases with B-cell ALL. The presence of both translocations in this patient's cells suggests a possible precursor B-lymphoblastic leukemia/lymphoma.
also been reported in another case with pre-B-ALL.\textsuperscript{18}
Because of the frequency with which a break is
detected at band q32 of chromosome no. 14 in Burkitt's
and non-Burkitt's lymphomas, it has been suggested
that an abnormality at this site may confer a proliferative advantage. It is known that chromosome no. 14
contains the immunoglobulin heavy chain gene cluster
at band q32.\textsuperscript{19} Recent studies have located the human
homolog of the \textit{myc} oncogene on chromosome no. 8 at
the site that is involved in the (8;14)(q24;q32) translo-
cation.\textsuperscript{20} It has been suggested that the \textit{c-myc} gene on
chromosome no. 8 and immunoglobulin heavy chain
Fig. 3. G-banded karyotype of the patient's peripheral blood cells.

...gene cluster on chromosome no. 14 become aligned in a 5'-to-5' head-to-head fashion as a result of the translocation. It is proposed that the level of expression of the c-myc gene is affected by the neighboring active immunoglobulin genes, and the normal regulatory control is lost, leading to a malignant transformation. It is of interest that this patient also had a t(14;18)(q32;q21). This translocation, in which the breakpoint at chromosome 14q32 is apparently identical to that found in the t(8;14), has been reported by Yunis et al. in the lymph nodes of 16 of 19 patients with follicular lymphomas. However, a combination of t(14;18) and t(8;14) has not been reported previously. It can be postulated that there is a human homolog of an oncogene on chromosome no. 18, which, by analogy with the t(8;14), may be affecting the Ig heavy chain gene cluster on chromosome no. 14.

This patient's age on presentation, high peripheral blast count, and karyotypic abnormalities are all associated with a poor prognosis. It has been shown that with the 8;14 translocation, immunoglobulin secretion is normally controlled by the unaffected chromosome 14. It is possible that abnormalities of both no. 14 chromosomes, as in this patient, confer a particularly poor prognosis. However, the true prognostic implications of this will be discerned only when the results of the karyotypic analysis of a larger group of patients with ALL become available.

ACKNOWLEDGMENT

We are very grateful to Dr. Marina Seabright, Wessex Regional Cytogenetics Unit, for helpful discussions.

REFERENCES

6. Yunis JJ, Oken MM, Kaplan ME, Ensrud KM, Howe RR,


15. ISSN: An international system for human cytogenetic nomenclature. Birth Defects 14:8, 1978


Common ALL with pre-B-cell features showing (8;14) and (14;18) chromosome translocations

GJ Mufti, TJ Hamblin, DG Oscier and S Johnson