Pre-B Cell Acute Lymphoblastic Leukemia in the Newborn

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Leukemia in the newborn is an infrequent disease that has not been well defined using modern laboratory techniques. We describe two infants, one at birth and one at four weeks, with acute lymphoblastic leukemia. The blasts from each patient were studied in great detail, using a battery of cytochemical and immunologic procedures in addition to ultrastructural studies. Immunologic cell marker studies, not previously reported in congenital leukemia, showed the lymphoblasts from each infant to be of the pre-B cell phenotype. Each infant relapsed, one after a 17-week clinical remission and the other after a 44-week remission. The former has died while the latter is in a second remission. The subtype of pre-B cell acute lymphoblastic leukemia (ALL) which in childhood appears to confer an unfavorable prognosis, may have the same significance in neonatal ALL.

Case 1, SE

A 3-kg full-term female infant was noted, shortly after birth, to have the following peripheral blood count: hematocrit 0.51 g/dL, platelets 10 × 10⁹/L, WBC 114 × 10⁹/L with 53% blasts. She was lethargic, but her physical examination was unremarkable, except that the liver was palpable 4 cm beneath the right costal margin. There were no features suggestive of Down's syndrome. On the second hospital day, a bone marrow aspiration revealed a hypercellular specimen with 80% lymphoblasts. Over the course of the next few days, her WBC increased to 132.4 × 10⁹/L with 91% blasts. She was successfully induced into complete remission, as documented by bone marrow aspiration, following a four-week course of prednisone, vincristine, daunomycin, l-asparaginase, and cyclophosphamide. He then received a period of intensification with cytosine arabinoside, thioguanine, vincristine, daunomycin, l-asparaginase, and cyclophosphamide. He then received a period of intensification with cytosine arabinoside, thioguanine, l-asparaginase, and methotrexate, plus intrathecal methotrexate. Remission had been sustained for 11 months on multiagent maintenance chemotherapy, when he experienced a bone marrow relapse. He is currently in his second remission.

Case 2, VB

A previously healthy 8-week-old male was noted to have pallor and hepatosplenomegaly during a routine physical examination. There were no features suggestive of Down's syndrome. His peripheral blood count revealed the following: hemoglobin 5.6 g/dL, platelet count 80 × 10⁹/L, and WBC 146 × 10⁹/L with 94% blasts. A bone marrow aspiration revealed a hypercellular specimen with 75% lymphoblasts. Complete remission, documented by bone marrow aspiration, was achieved following four weeks of induction therapy with prednisone, vincristine, daunomycin, l-asparaginase, and cyclophosphamide. He then received a period of intensification with cytosine arabinoside, thioguanine, l-asparaginase, and methotrexate, plus intrathecal methotrexate. Remission had been sustained for 17 weeks on multiagent maintenance chemotherapy when she suffered a bone marrow relapse. She expired at age 7 months.

MATERIALS AND METHODS

Peripheral blood and bone marrow aspirate specimens were available for study from both patients. In addition to Wright's stain, the following cytochemical procedures were done: Sudan black B, peroxidase, nonspecific esterase (using alpha-naphthyl butyrate as substrate),13 and acid phosphatase. Terminal deoxynucleotidyl transferase (TdT) activity, using the fluorescent antibody technique,14 was also measured. Commercial monoclonal antibody was used for the detection of T cell antigen.15

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An indirect immunofluorescent technique with a pan-T cell monoclonal antibody was used for the detection of T cell antigen.15 Monoclonal antibodies used were: HTA (Hybritech, Inc, La Jolla, Calif), and MO (Coulter Diagnostics, Hialeah, Fla). Common ALL antigen (J5, CALLA) was provided by Dr J. Ritz, Sidney Farber Cancer Institute, Boston.16 Cells were incubated with sheep red blood cells (SRBCs) and examined for spontaneous E rosette formation. Material and methods.
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formation. Cyto centrifuge preparations of the E rosettes were Wright's stained.

Ultrastructural studies were performed on buffy coat cells from peripheral blood using standard electron microscopic technique. The blasts were also examined for ultrastructural localization of endogenous peroxidase. Cytogenetic studies were performed on buffy coat bone marrow aspirate using standard cytogenetic techniques.

RESULTS

Using the French-American-British (FAB) classification for acute leukemia, the blasts in the peripheral blood and bone marrow in each case showed typical L2 type morphology. All cytochemical studies were negative. The ultrastructural features were consistent with lymphoblasts, and no peroxidase-positive granules were noted. A summary of the immunologic studies performed and the results obtained in each case is presented in Table 1. The blasts from both patients had the immunologic phenotype of pre-B cells. In case 1, the immunologic studies done on blasts from the bone marrow aspirate at relapse showed identical features to those obtained at time of diagnosis. Cytogenetic studies performed on bone marrow from case 1 were normal.

DISCUSSION

Most of the reports of congenital and neonatal leukemia in both Down's and non-Down's syndrome infants have consisted of isolated case reports or small numbers of cases with literature reviews. The accuracy of the diagnoses, however, varied with the methods available at the time. Thus, in many of the cases reported, it is difficult to determine what type of leukemia was present. Complicating this are reports of a transient myeloproliferative condition among some infants with Down's syndrome that simulates leukemia.

Almost all previous reports of congenital and neonatal leukemia have relied on morphological criteria alone to characterize the leukemic cell population. It is now apparent that a battery of cytochemical and immunologic techniques are sometimes necessary to separate lymphoblastic from myeloblastic leukemia and to distinguish important prognostic subgroups of acute lymphoblastic leukemia (ALL). The subdivision of ALL into immunologic subtypes has revealed a group of 15% to 20% that mark as T cells, a group of 1% to 5% that mark as B cells, and the remainder that do not mark as either B or T cells.

The immunologic subtype of pre-B cell ALL has been defined as lymphoblastic leukemia with the blasts having intracytoplasmic immunoglobulin M (ClgM) in at least 10% of neoplastic cells, but no surface immunoglobulin (Slg) and no evidence of B or T cell maturity. The common ALL antigen (CALLA) is present in the majority of cases of pre-B cell ALL. The lymphoblasts in our patients, however, were CALLA negative. This is an unusual finding, since pre-B cell ALL is assumed to be a subset of “common” ALL. In both patients, the lymphoblasts were strongly TdT positive, indicating that TdT is expressed early in the B cell lineage.

The precise characterization of the type of acute leukemia present is extremely important, in that it directs the specific therapy and greatly influences the prognosis. For children with acute lymphoblastic leukemia, prognosis and therapy are influenced significantly by parameters established at diagnosis, such as age and WBC. Age under 1 year and a WBC over 50 x 10⁹/L are both considered unfavorable prognostic indicators at the time of diagnosis. Markedly elevated WBCs are common at the time of diagnosis in newborns with acute leukemia. Although some reports indicate that children with pre-B cell ALL may do as well as those with the non-B, non-T cell subtype, other reports indicate that pre-B cell ALL has an unfavorable prognosis with early relapse. Our patients both had early relapse, and one subsequently died. This is consistent with the latter group of reports.
less of age at diagnosis. Further study utilizing all of the modern laboratory methodology and a larger cohort of neonates with acute leukemia is needed to precisely define prognosis and the factors that influence it.

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