Acute Leukemia Occurring During Chronic Lymphocytic Leukemia

By Peter McPhedran and Clark W. Heath, Jr.

The concept of “blast crisis” in chronic leukemia implies a single disease process advancing from chronic to acute phase. How often this happens in chronic lymphocytic leukemia, or whether it happens at all, is uncertain. Unlike chronic granulocytic leukemia, chronic lymphocytic leukemia does not often end in acute leukemia. While it is possible that occasional cases may have a true blast phase, the relative significance of such events can only be assessed by: (1) studying the cell types of acute leukemia occurring in chronic lymphocytic leukemia, and (2) measuring the frequency with which such cases occur.

This report describes two instances of acute leukemia in patients with chronic lymphocytic leukemia, examines the incidence of such cases in a general population, and reviews the frequency and cytology of similar cases reported in the medical literature.

Case Reports

E.H. (GBH 247347), a 75-year-old woman, went to her doctor for pain in her back and abdomen in March 1957. Her white count at that time was 8350 per cu. mm. and the differential included 70 per cent lymphocytes. Her symptoms were attributed to osteoporosis. Between 1957 and 1961 the patient had numerous diagnostic x-rays: four sets of chest films, two sets of lumbar spine films, a sinus series, a gall bladder series, two upper gastrointestinal series, and two barium enemas.

In the spring of 1961, E.H. went to her physician with a cough. A white count in May 1961 was 6200 per cubic millimeter with 84 per cent mature lymphocytes. A bone marrow aspirate was cellular, mature lymphocytes accounting for 43 per cent of nucleated elements. Neither lymph nodes nor spleen were enlarged. A diagnosis of “aleukemic chronic lymphocytic leukemia” was made.

Treatment with chlorambucil was started in May 1961 and continued for the next two years. During these two years E.H.’s hemoglobin and platelet counts remained normal and...
her white counts ranged between 4000–8000 per cubic millimeter with 60–90 per cent lymphocytes. Occasional blasts were noted in her peripheral blood as early as October 1961. A second bone marrow examination in January 1963 (Fig. 1A) showed diffuse infiltration with lymphocytes. In the summer of 1963, E.H. developed weakness and easy bruising, and in October she had 32 per cent blasts in her peripheral blood. Bone marrow examination early in November 1963 revealed "striking lymphocytic infiltration with a high percentage of lymphoblasts." A diagnosis of "chronic lymphocytic leukemia with transformation to lymphoblastic leukemia" was made (Fig. 1B).

Therapy was changed to 6-mercaptopurine and prednisone. A falling hemoglobin necessitated transfusion. Remission was not achieved and she died in December 1963.

J.H. (EUC No. 99–317), a 38-year-old white male, first noted intermittent swellings in his neck in 1961. In November 1963, he developed masses in both inguinal areas. Blood studies on December 13, 1963, revealed a white count of 33,900 per cu. mm. with 90 per cent lymphocytes. After biopsy of inguinal and axillary masses the patient was told he had "leukemia of the lymph nodes." In December 1963 he received 45 r. total body ("spray") radiation, and during January and early February 1964, he received 200 r. to inguinal areas and 300 r. to his spleen. In February 1964, after the x-ray therapy, J.H. was found to have pancytopenia with splenomegaly and marked enlargement of cervical, axillary, and inguinal lymph nodes. A sternal marrow aspirate was markedly hypocellular with 96 per cent mature lymphocytes. Touch preparations from bone marrow biopsy were hypercellular with 70–75 per cent lymphocytes (Fig. 1C). A diagnosis of chronic lymphocytic leukemia was made. The pancytopenia was tentatively attributed to radiation therapy. He was treated with prednisone for three months, then chlorambucil for three years. Although his hemoglobin and white count returned to normal ranges, he remained thrombocytopenic with a relative lymphocytosis. Lymphadenopathy waxed and waned. In August 1967, blasts were noted in the peripheral blood, and bone marrow specimens obtained in August and September contained numerous blasts (Fig. 1D). A diagnosis of "blast crisis of chronic lymphocytic leukemia" was made. Treatment with prednisone and...
6-mercaptopurine was followed by disease remission. Bone marrow in October showed erythroid hyperplasia. In February 1968, the patient relapsed and died of acute leukemia.

Bone marrows from both patients at the time of diagnosis of acute leukemia were reviewed by the authors and by three independent hematologists. Most nucleated cells in E.H.’s bone marrow were large and immature with one or more prominent nucleoli and, in many cells, abundant cytoplasm containing granules. Moderate numbers of myelocytes, metamyelocytes, band neutrophils, and polymorphonuclear leukocytes were also present. Red cell precursors showed megaloblastoid changes. The consensus was that this bone marrow reflected acute leukemia of either granulocytic or reticulum cell series. In J.H.’s bone marrow, nearly all nucleated cells were large and vacuolated with scant cytoplasm and rare granules. It was agreed that these cells represented a primitive leukemia. However, the blasts were variously identified as stem cells, lymphoblasts, and lymphoreticular cells.

**INCIDENCE SURVEY**

These two cases were the only ones of their kind identified among 340 cases of chronic lymphocytic leukemia in a registry of leukemia cases maintained in Atlanta, Georgia. This registry includes all cases diagnosed in the five-county metropolitan Atlanta area between 1956 and 1966. It is supplemented with cases identified from death certificates of all persons dying in Atlanta (1956–1966), and in all of Georgia (1965–1966). Clinical followup information through contacts with hospitals and physicians is obtained regularly for residents of the Atlanta area. One of the two cases occurred in an Atlanta resident (E.H.); the other lived in another city.

Since an accurate estimate of acute leukemia incidence in cases of chronic lymphocytic leukemia requires a series of cases with uniform clinical followup, analysis of incidence was restricted to all cases in white residents of metropolitan Atlanta (222 cases). In this group, 0.12 cases of acute leukemia might be expected to occur during the 11-year period of observation (1956–1966). (This estimate of expected incidence is based on age-specific death rates in the United States for leukemia in the white population in 1960, adjusted to the proportion of deaths coded as monocytic and acute leukemia.1,2) Since only one case of acute leukemia was observed in this group of patients, incidence of acute leukemia cannot be said to exceed significantly that experienced in the general population.

**COMMENT**

The occurrence of acute leukemia in patients with chronic lymphocytic leukemia has been described in six prior reports. Four of these reports give an estimate of the frequency of acute leukemia in chronic lymphocytic leukemia, and three describe cytologic features of the acute leukemia cases. Diamond et al.3 described two cases of acute leukemia (of unstated cell type) among 53 patients with chronic lymphocytic leukemia. Lawrence et al.4 reported two patients with acute leukemia among 100 chronic lymphocytic leukemia patients. Osgood and Seaman5 saw seven instances of “acute terminal phase” of chronic lymphocytic leukemia among a group of 102 patients. In a later report,
Osgood observed five cases of monoblastic leukemia in a group of 201 patients with chronic lymphocytic leukemia. Lortholary et al. have described a single patient who developed myeloblastic leukemia after chronic lymphocytic leukemia while Boggs et al. mention a case of lymphoblastic leukemia in a similar patient. In all but the last report, each patient with acute leukemia had received prior treatment with radioactive phosphorus.

Less than four per cent (16 of 456) of patients described by Diamond, Lawrence, and Osgood, and less than one per cent (2 of 340) of patients in the present series, developed acute leukemia. The difference between these two frequencies may well reflect greater selection of patients in past published reports, together with the fact that virtually all such patients received radio-phosphorus. It is obvious, however, that the proportion of persons with chronic lymphocytic leukemia who develop acute leukemia is small compared to the proportion of persons with chronic granulocytic leukemia who experience blast crisis. Whether or not acute leukemia is at all more frequent in patients with chronic lymphocytic leukemia than in the general nonleukemic population cannot be told from current data. While the rate of acute leukemia among cases in metropolitan Atlanta indicates a low level of incidence, too few cases were studied to allow any conclusions. It is likewise impossible to say whether the data of Diamond, Lawrence, and Osgood represent increases over expected incidence (allowing for effects of radiotherapy), in the absence of information concerning ages of patients and duration of follow-up.

The rarity of acute leukemia in chronic lymphocytic leukemia, together with the variable cytology of reported cases, suggest that they result from the same leukemogenic influences which affect the general population. While occasional cases of lymphoblastic leukemia may well represent a true blast phase of chronic lymphocytic leukemia, it seems quite possible that many cases of acute leukemia superimposed on chronic lymphocytic leukemia are separate malignant processes unrelated to the underlying chronic leukemia.

**Summary**

Acute leukemia occurred in two of 340 persons with chronic lymphocytic leukemia listed in a registry of leukemia cases among residents of Georgia. One case was acute myeloblastic leukemia; the cell type of the other was disputed. Before onset of acute leukemia, one patient had had numerous diagnostic x-rays, while the other had received therapeutic radiation. These data and previous case series indicate that acute leukemia in patients with chronic lymphocytic leukemia is rare, has no consistent cell type, and often follows exposure to therapeutic radiation. It seems possible that such cases of acute leukemia often represents a second malignancy than a true blast phase of chronic lymphocytic leukemia.

**Acknowledgments**

We wish to thank Drs. James W. Lea and W. Harrison Reeves, who provided clinical information on J.H. and E.H., and Drs. Stuart C. Finch, Charles M. Huguley, and William C. Moloney, who reviewed the bone marrow slides.
REFERENCES

Acute Leukemia Occurring During Chronic Lymphocytic Leukemia

PETER McPHEDRAN and CLARK W. HEATH, JR.