

Acute Lymphoblastic Leukemia Following Hodgkin's Disease

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ABSTRACT

Over 100 instances of acute leukemia have been reported in the course of Hodgkin's disease. The type of leukemia almost always is nonlymphoblastic. Only five well documented cases of acute lymphoblastic leukemia (ALL) have been found by us in the world literature. One case who developed ALL six years after intensive radiotherapy for Hodgkin's disease is herewith reported. The patient responded to treatment with Predisone, Vincristine and intrathecal methotrexate and maintained a complete remission on 6-mercaptopurine for nine months. When last seen, the bone marrow revealed a mild increase in blasts indicative of an early relapse.

The incidence of second malignancy developing in the course of Hodgkin's disease (HD) has been reported from 1.6 to 2.2 percent.^{1,13,14} Acute non-lymphoblastic leukemias (ANLL) are among the commonest second tumors.^{2,14} There is some controversy in the literature whether acute lymphoblastic leukemia (ALL) occurs in the course of Hodgkin's disease.² A report is presented here of a 35 year old patient who developed ALL six years after intensive radiotherapy for HD.

Case Report

H. F., a 35 year old white male was in good health until six years ago when he noted a small lump in the right anterior

cervical area. He was treated initially with penicillin but had no significant improvement. An excisional node biopsy was performed and a diagnosis of Hodgkin's disease, mixed cellularity, was made. The general architecture of the lymph node was partially effaced, though several germinal centers were still present. Most of the node consisted of sheets of lymphocytes with interspersed plasma cells, eosinophils and histiocytes. Several atypical histiocytes and Reed-Sternberg cells were identified (figure 1). The patient underwent exploratory laparotomy, splenectomy, open liver biopsy, multiple intraabdominal node biopsies and bone marrow biopsy. No other evidence of Hodgkin's disease was found and the patient was classified as clinical stage 1-A. All blood studies were unremarkable. External cobalt radiation therapy delivered 4,000 rads utilizing the mantel technique.

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The patient was followed for six years and had been asymptomatic and in remission until June, 1977 when he became anemic. At this time the patient noted the onset of left flank pain and fever. On admission to High Plains Baptist Hospital, the patient was found to have a white blood cell count of 16,300 with 1 percent bands, 11 percent segmented neutrophils, 21 percent lymphocytes, 1 percent monocytes and 66 percent blasts. Hemoglobin was 7.9 g, hematocrit was 22 and platelets were within normal limits. Physical examination showed no lymphadenopathy or hepatomegaly. Numerous lymphoblasts and prolymphocytes were present in the peripheral blood. Bone marrow aspirate showed a marked proliferation of lymphocytic precursors. Megakaryocytes were adequate. A diagnosis of acute lymphoblastic leukemia was made (figure 2).

Shortly thereafter, the patient was referred to The Methodist Hospital in Houston. Repeat bone marrow biopsy was hypercellular (95 percent) with approximately 67 percent of the population consisting of peroxidase and Sudan black B negative blasts. PAS stain showed an occasional blast with coarse PAS positive granules. The morphology and cytochemistry confirmed the diagnosis of acute lymphoblastic leukemia.

The patient was given chemotherapy with Vincristine and prednisone for one month. He also received intrathecal methotrexate. On 7/18/77, the bone marrow and peripheral blood showed no increase in blasts. The patient was felt to be in complete remission. He was started on maintenance chemotherapy with 6-mercaptopurine and was again given intrathecal methotrexate. On discharge, the prednisone was tapered and the patient was subsequently maintained on 6-mercaptopurine.

Complete blood counts were made at weekly intervals—the patient was followed by a hematologist with weekly

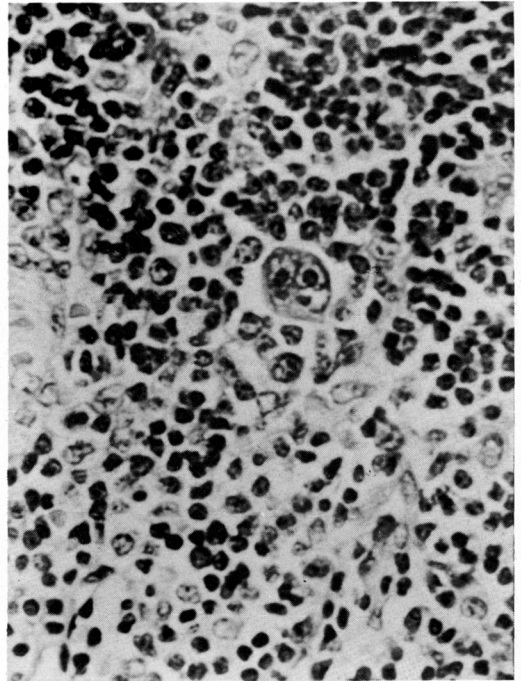


FIGURE 1. Lymph node biopsy. Normal architecture replaced by sheets of lymphocytes, atypical histiocytes, eosinophils and Reed-Sternberg cell. (H&E \times 500).

CBC's. The patient was readmitted to our hospital on 9/6/77 because of weakness

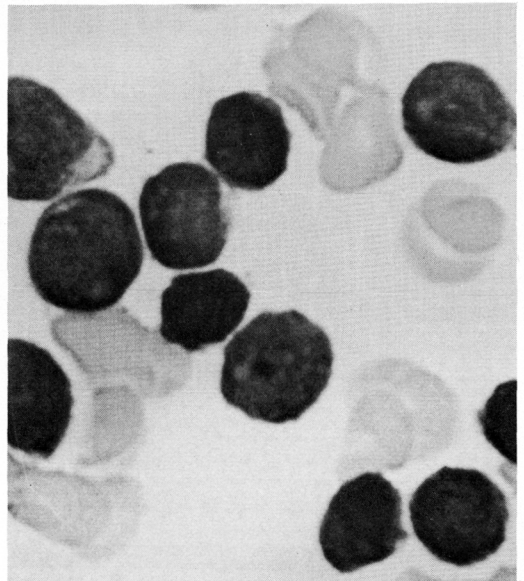


FIGURE 2. Lymphoblasts in bone marrow aspirate. (Wrights stain \times 1250).

and weight loss. Admission laboratory data showed a hematocrit of 31, white blood cells (WBC) 3,000 and 450,000 platelets. Bone marrow aspiration and biopsy showed a hyperplastic marrow without any increase in blasts, and the patient was felt to be still in remission. He was again discharged on 6-mercaptopurine.

The patient was again seen on 1/3/78 without complaints and with a hemoglobin of 16, hematocrit of 45, WBC of 6400 with no blasts and platelets of 351,000. He was noted to have no progressive adenopathy or hepatosplenomegaly. The patient was admitted on 12/5/78 to evaluate the state of his leukemia. His CBC showed a hematocrit of 41, WBC 5,300 with normal differential, adequate platelets and no blasts. The bone marrow revealed an orderly myelopoiesis and erythropoiesis. Nine percent blast forms were noted which could represent an early relapse. The patient was given cytoxan 1000 mg intravenously and was placed on 4 mg of Decadron twice a day for 28 days. He was advised to continue cytoxan at monthly intervals and to report to our hospital after three months.

Discussion

More than 100 instances of Hodgkin's disease and acute leukemia have been reported in the world literature.^{2,4,15} In the majority of patients the type of leukemia is

ANLL. Only five reported cases of acute lymphoblastic leukemia occurring in the course of Hodgkin's disease were found by us.^{3,7,8,9,10} In reported cases where ALL occurred simultaneously with HD and the cases where a diagnosis of Stem cell leukemia was made are not included in the present study.

Bloomfield and Brunning² in a critical review of English literature reported 17 cases of ANLL. The instances of ALL following Hodgkin's disease, in their opinion, were poorly documented and they questioned if ALL ever occurs in the course of HD.² Both HD and ALL may, at times, present a diagnostic challenge. HD may be difficult to differentiate from non-Hodgkin's lymphoma (NHL), since Reed-Sternberg cells have been seen in lymph nodes and bone marrow from patients with NHL.^{6,12,17,18} Moreover, NHL frequently peripheralizes into acute lymphoblastic leukemia. Thus, in all instances of ALL following HD, the diagnosis of HD should be reviewed.

Likewise, it is often difficult to differentiate ALL from ANLL by light microscopy alone and ancillary diagnostic studies are necessary in such cases. Cytochemical stains may provide some help.¹⁶ In table I are depicted the differential staining characteristics of blasts in acute leukemias. Typically, the lymphoblasts are peroxidase, Sudan black B and naphthol AS-D chloracetate esterase negative. Naphthyl acetate esterase is usually negative but may, rarely, give a faint positive stain. PAS stain is perhaps the most characteristic. In most cases of ALL, at least a few lymphoblasts show a PAS positive (block) cytoplasmic staining.

Terminal deoxynucleotidyl transferase (Tdt) levels are sometimes of great value. This enzyme catalyzes the polymerization of deoxyribonucleotides on the hydroxyl ends of oligo or poly deoxyribonucleotides in the absence of a DNA template. High levels of Tdt have been reported in the cells of some patients with ALL. High

TABLE I

Cytochemical Staining of Blasts in Acute Leukemia

Stain	Lympho- blasts	Myelo- blasts	Mono- blasts
Peroxidase	-	++	+
Sudan black B	-	++	+
Naphthol AS-D chloracetate esterase	-	++	-
Naphthyl acetate esterase	±	-	++
PAS	+ block	- to + diffuse	- to + diffuse

TABLE II

Acute Lymphoblastic Leukemia (ALL) Following Hodgkin's Disease (HD)

Case No.	Reference	Sex & Age at Onset of HD	Histologic Type of HD	Therapy	Interval from HD to ALL	Interval from ALL to Death
1	9	F 18 years	Mixed cellularity	Radiotherapy	2 years	3 months
2	8	M 57 years	Not given	Radiotherapy	8 years	Not given
3	10	Not given	Not given	Radiotherapy & chemotherapy	6 years	Not given
4	3	F 34 years	Mixed cellularity	Radiotherapy & chemotherapy	3½ years	6 weeks
5	7	M 3 years	Mixed cellularity	Chemotherapy	6¼ years	5 months
6	Present report	M 29 years	Mixed cellularity	Radiotherapy	6 years	6 months (living)

levels are found in thymus but very low levels are seen in normal marrow and in other leukemias.¹¹

Rosner and Grunwald¹⁵ reviewed four cases of ALL following Hodgkin's disease. Falkson⁷ reported one case, and our case is added to the list. In table II are summarized the salient points of these six cases. There are three males, two females and, in one case, sex is not stated. The mean age is 30 years with a range from three to 57 years. It is interesting to note that in four cases where microscopic description was available, the histological classification was mixed cellularity type of HD. Three patients in this series received radiotherapy, one received chemotherapy and the other two received both radiotherapy and chemotherapy. ALL developed in these patients from two to eight years (mean 5.3 years) after the diagnosis of HD.

The relationship between Hodgkin's disease and acute leukemia (ANLL or ALL) remains undefined. Whether the disease renders the host more susceptible or the intensive therapy is in some way responsible for the development of second tumor is not entirely clear. Apparently there are no characteristic features of Hodgkin's disease which predispose to second malignancy.¹⁵ It has been noted that the majority of these patients have had intensive radiotherapy or chemo-

therapy or both.⁵ A genetic predisposition and suppressed immunity may also contribute their share.

Summary

A patient who developed Hodgkin's disease, mixed cellularity type at the age of 29 has been described by the present authors. He was treated intensively with radiotherapy. Six years later he developed acute lymphoblastic leukemia. The blasts from his bone marrow and peripheral blood, morphologically resembled lymphoblasts, were peroxidase, Sudan black B and esterase negative. PAS showed a small population of PAS positive block granularity in the cytoplasm. The patient responded to treatment with prednisone, Vincristine and intrathecal methotrexate and maintained a complete remission with 6-mercaptopurine for nine months when the bone marrow showed an early relapse. He was placed on cytoxan at monthly intervals and was advised to report in three months for further evaluation.

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