CHRONIC LYMPHOCYTIC LEUKEMIA IN HODGKIN'S DISEASE

Report of a Case and Review of the Liteature

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We recently observed the occurrence of chronic lymphocytic leukemia in a patient with Hodgkin's disease of mixed cellularity type involving the right inguinal region who had been treated with radiation therapy. The patient developed classical chronic lymphocytic leukemia with generalized lymphadenopathy, splenomegaly, and lymphocytosis after a 13-year remission of Hodgkin's disease. In vitro lymphocyte response to phytohemagglutinin showed the depressed and delayed DNA synthesis, and immunoglobulin determination showed marked deficiency of IgG and slight deficiency of IgA, usually seen in chronic lymphocytic leukemia. The medical literature contains reports of Hodgkin's disease complicating chronic lymphocytic leukemia in 17 instances and reports of chronic lymphocytic leukemia complicating Hodgkin's disease in only two instances. This association of Hodgkin's disease and chronic lymphocytic leukemia probably represents the occurrence of two separate diseases.

HODGKIN'S DISEASE AND CHRONIC LYMPHOCYTIC leukemia are usually regarded as two distinct neoplastic diseases, with no known common etiologic relationship. The occurrence of Hodgkin's disease in patients with chronic lymphocytic leukemia has been rarely noted; 17 such cases were reported.[1–3,11,13–17,19,20,23,24,27] The occurrence of chronic lymphocytic leukemia complicating Hodgkin's disease is extremely rare, and only two reports[25,27] were found in the medical literature. The present report describes a patient with Hodgkin's disease who was in complete remission for 13 years, then developed classical chronic lymphocytic leukemia.

CASE REPORTS

H.G. (83083), a 35-year-old Caucasian man, first noted a painful swelling in the right groin in December 1954. He was found to have right inguinal lymphadenopathy. An excisional biopsy of the lymph node was performed, and he was referred to the Roswell Park Memorial Institute in February 1955. Histologic sections of the biopsied lymph node were typical of Hodgkin's disease. The patient did not have systemic manifestations.

Physical examination revealed no significant peripheral lymphadenopathy or hepatosplenomegaly.

Pertinent hematologic data are shown in Table 1. An initial complete blood count was as follows: the hemoglobin was 13.2 g/100 ml, the white blood cell count was 5,750/mm^3, with 50% polymorphonuclear cells and 39% lymphocytes, and the platelet count was 237,500/mm^3. Chest roentgenogram showed no hilar or mediastinal lymphadenopathy.

The patient was given irradiation (2780 rads tumor dose) to the right inguinal and femoral areas from March 3 through March 18, 1955. He was seen in the clinic periodically and remained in remission. Several chest roentgenograms were normal.

In 1965, following more than a 10-year remission, the original histologic sections were reviewed and the diagnosis of Hodgkin's disease was confirmed. Blood count on each clinic visit was within normal limits. The hematocrit was 43%, the hemoglobin was 12.4 g/100 ml, the white blood cell count was 5,456/mm^3, with 85% polymorphonuclear cells and 14% lymphocytes, and the platelet count was 121,975/mm^3 in March 1967.

On March 22, 1968, physical examination revealed bilateral cervical and axillary lymphadenopathy. Hemoglobin was 12 g/100 ml, the

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TABLE 1. Summary of Clinical Data

Date	Lymphadenopathy	Hemoglobin g/100 ml	Platelets $10^3/mm^3$	White Blood Cells $10^3/mm^3$	Lymphocytes (Per cent)
2/ 8/55		13.2		5.8	39
6/30/58		12.3	192.5	4.4	29
4/ 4/61		13.5	200.0	8.2	27
1/ 7/65		14.3	200.0	6.9	20
3/23/67		12.4	122.0	5.5	14
3/22/68	Moderate bilat. cerv. & axillary	13.0	97.4	20.3	89
4/30/68	Para-aortic & iliac	12.0	131.1	40.8	92
9/24/68		11.0	118.3	6.3	76
2/14/69		14.0	79.0	29.5	59
10/17/69	Minimal cerv. & axillary	9.8	98.7	78.7	93
2/13/70		12.7	60.0	126.4	98

white blood cell count was 20,300/mm^3, with 89% lymphocytes. A bone marrow aspiration on April 12, 1968, showed normal cellularity with nearly 80% mature lymphocytes. Some immature forms were also seen. A lymphogram showed enlarged and foamy inguinal, iliac, and para-aortic lymph nodes. On April 30, 1968, the spleen was palpable 4 cm and the liver was palpable 2 cm below the respective costal margins. A cervical lymph node biopsy was performed on April 23, 1968. The histologic findings were typical of chronic lymphocytic leukemia or lymphosarcoma, without evidence of Hodgkin's disease.

The white blood cell count gradually increased further to 40,800/mm^3, with 92% lymphocytes on April 30, 1968. He was given chlorambucil 6 mg and prednisone 45 mg orally daily from April 30, 1968 to July 11, 1968, with an excellent response, characterized by disappearance of hepatosplenomegaly, peripheral lymphadenopathy, and marked shrinkage of dye-filled para-aortic, iliac, and inguinal lymph nodes. The dose of prednisone was reduced to 15 mg daily on July 12, 1968. The hemoglobin was 12.3 g/100 ml, the white blood cell count was 8,500/mm^3 and the platelet count was 72,000/mm^3 on September 10, 1968. The dose of chlorambucil was reduced to 2 mg daily. A punch biopsy, in December 1968, of a small skin lesion on the left post-auricular fold revealed basal cell carcinoma. The lesion was electrocauterized, with an excellent result. When last seen in February 1970, the patient was asymptomatic, without lymphadenopathy or hepatosplenomegaly.

HISTOLOGIC FINDINGS

The lymph node section which was biopsied in 1955 showed diffuse reticulum cell hyperplasia entirely obscuring the normal lymphoid structure. Most of the reticulum cells were irregular, and some of them were anaplastic. A few lobulated, binucleated, or even multinucleated reticulum cells were found; some of them resembled Sternberg-Reed cells. The eosinophils were occasionally seen. Fibrosis was not found (Fig. 1). These findings are typical of Hodgkin's disease, mixed cellularity type.

Sections of lymph node biopsied in 1968 showed a severe distortion of normal architecture of lymph node by a pronounced lymphoproliferative process. Both the sinuses and a considerable portion of the cortex were infiltrated with small lymphocytes which had taken over some of the follicles; in some areas, residual follicles were encountered. A pronounced lymphoid infiltration of the node capsule and lymphoid spillage into the surrounding fatty tissue were noted. A large number of lymphocytes was found in the small vessels of the lymph node (Fig. 2). There was no evidence of Hodgkin's disease.

IMMUNOLOGIC STUDIES

The lymphocyte response to phytohemagglutinin (PHA) was performed according to the method previously reported.[8] DNA synthesis was maximal on third day of lymphocyte culture in normal individuals. DNA synthesis was markedly depressed on the third day, and it was maximal on seventh day of lymphocyte culture in this patient. This depressed and delayed PHA response is usually seen in typical chronic lymphocytic leukemia.

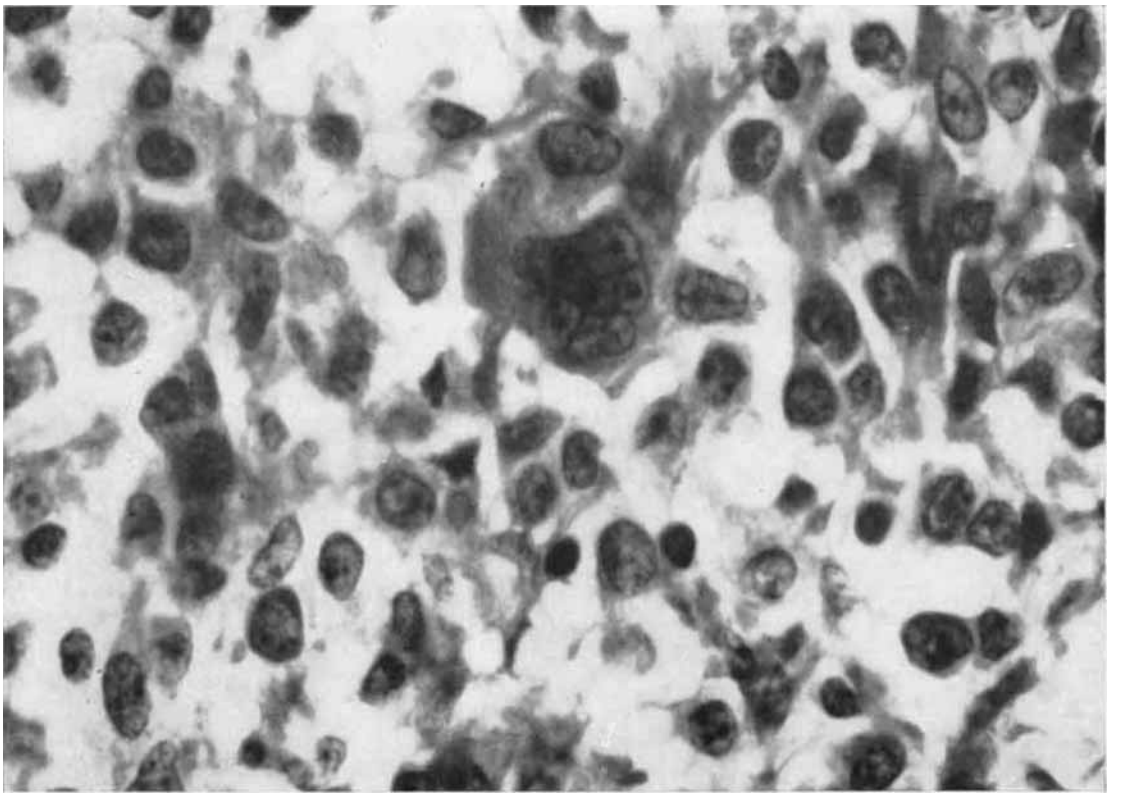

FIG. 1. Lymph node biopsy showing Hodgkin's disease, mixed cellularity type with multinucleated Sternberg-Reed cell (H and E, ×2700).

Purified protein derivative (PPD), intermediate strength, and mumps skin tests were positive during the period 1964 through 1968, when Hodgkin's disease was in remission. This delayed skin test reactivity remained present when the patient developed chronic lymphocytic leukemia; however, both skin tests became negative 6 months after prednisone and chlorambucil administration was initiated.

The serum electrophoretic pattern was normal with 1.1 g/100 ml gamma globulin prior to the onset of chronic lymphocytic leukemia. Hypogammaglobulinemia (700 mg/100 ml) was observed after the diagnosis of chronic lymphocytic leukemia was established.

Immunoglobulin determination was performed according to the method of Fahey and Lawrence.[5] IgG was 445 mg/100 ml, which is significantly lower than the normal value (1200 ± 300 mg/100 ml). IgA was 125 mg/100 ml, which is slightly lower than the normal value (288 ± 121 mg/100 ml). IgM was 54 mg/100 ml, which is within normal limits (80 ± 29 mg/100 ml).

DISCUSSION

This patient with Hodgkin's disease of mixed cellularity type was in remission for 13 years, then developed classical chronic lymphocytic leukemia with generalized lymphadenopathy, splenomegaly, and lymphocytosis; a cervical lymph node biopsy was typical of chronic lymphocytic leukemia or lymphosarcoma. The delayed and depressed DNA synthesis of in vitro lymphocyte response to PHA, and hypogammaglobulinemia in this patient strengthen the diagnosis of chronic lymphocytic leukemia.

Review of the literature indicates that Hodgkin's disease complicating chronic lymphocytic leukemia outnumbered chronic lymphocytic leukemia complicating Hodgkin's disease. The true incidence of Hodgkin's disease developing in patients during the course of chronic lymphocytic leukemia is unknown. It seems to be very low; in this Institute, we have observed no Hodgkin's disease in approximately 400 patients with chronic lymphocytic leukemia. Moertel and Hagedorn[18] reported a study of

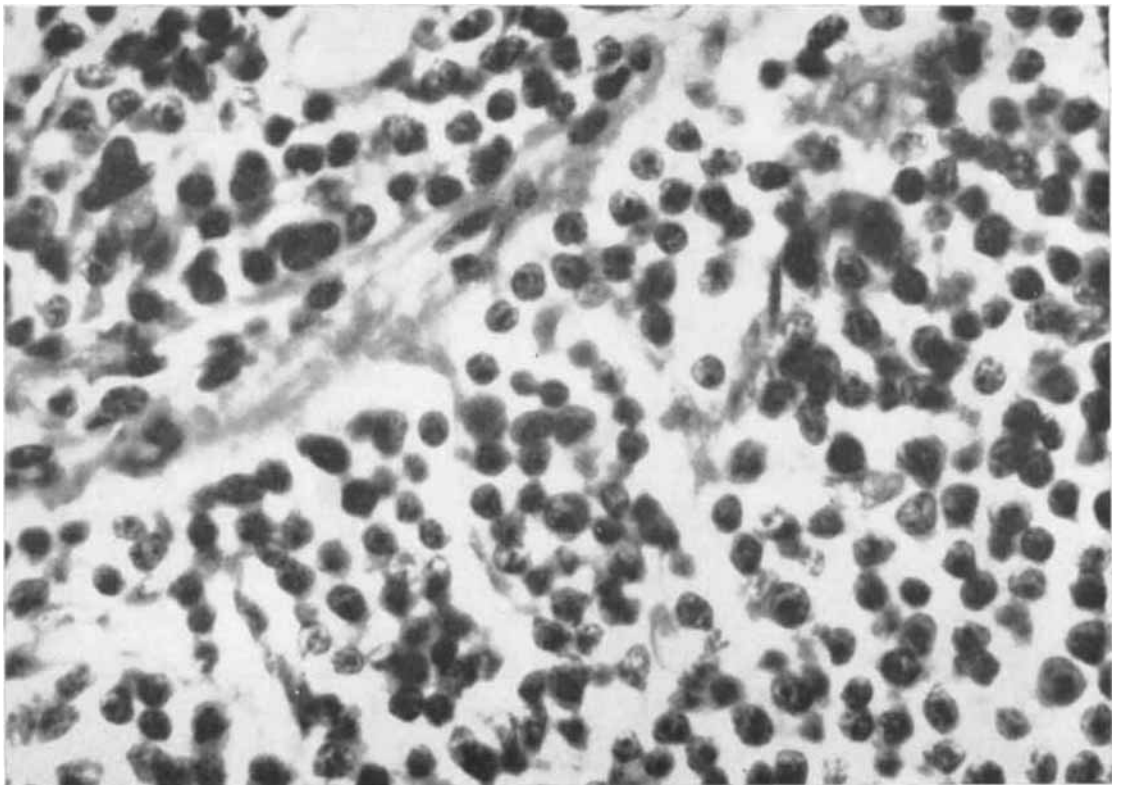

FIG. 2. Lymph node biopsy showing chronic lymphocytic leukemia (H and E, ×2700).

incidence of second malignant disease in 120 patients with lymphocytic leukemia and lymphoma. They observed no incidence of Hodgkin's disease in patients with chronic lymphocytic leukemia. Gunz and Angus[7] also did not observe any cases of chronic lymphocytic leukemia complicated by Hodgkin's disease in their national survey in England. Hyman[12] recently reported an increased incidence of neoplasm in association with chronic lymphocytic leukemia. The author found four instances of Hodgkin's disease complicating chronic lymphocytic leukemia or lymphosarcoma among 209 patients with these diagnoses; no case histories were given. We have found 17 well-documented cases of chronic lymphocytic leukemia complicated by Hodgkin's disease during a 40-year period (1928–1967) in the medical literature[1–3,11,13–17,19,20,23,24,27] (Table 2).

There were 12 male and 5 female patients. The diagnosis of Hodgkin's disease was made at autopsy in the majority of these cases. The granuloma type, found in 10 patients, was the most common among the different histologic cell types.

There are only a few reports in the literature regarding the incidence of second malignancy in patients with Hodgkin's disease. Razis et al.[21] reported the incidence of malignant and non-malignant diseases in 1,102 patients with Hodgkin's disease; there were no cases of chronic lymphocytic leukemia complicating Hodgkin's disease. We found only one case of chronic lymphocytic leukemia among 976 patients with Hodgkin's disease during 1928 through 1968 at our Institute. There are only 2 reports[25,27] of Hodgkin's disease complicated by chronic lymphocytic leukemia (Table 3). Warthin[25] described a 45-year-old woman with Stage III Hodgkin's disease of 4 years' duration who developed a blood picture of chronic lymphocytic leukemia just prior to her death. Autopsy of this case showed no lymphocytic infiltration in the lymph nodes, spleen, liver, or bone marrow, with the exception of lymphocytes in the blood vessels of these organs; Hodgkin's disease was found in each organ. It is possible that the lymphocytosis was a preterminal leukemoid reaction. Watson[27] reported a 65-year-old man with Stage III Hodgkin's disease complicated by

TABLE 2. Summary of Reported Cases of Hodgkin's Disease (HD) Complicating Chronic Lymphocytic Leukemia (CLL)

Case no.	Authors	Year	Sex	Age	Primary diagnosis	Secondary diagnosis	Time of secondary diagnosis
1	McCartney[17]	1928	F	52	CLL	HD	Postmortem
2	MacMahon & Parker[16]	1930	M	61	CLL	HD	Postmortem
3	Holler[11]	1931	M	41	CLL	HD	Postmortem
4	Craver[1]	1936	M	35	CLL	HD	Postmortem
5	Watson[27]	1938	M	67	CLL	HD	Postmortem
6	Seife et al.[23]	1951	M	76	CLL	HD	Postmortem
7	Krim et al.[14]	1952	M	67	CLL	HD	Antemortem
8	Epstein[3]	1956	F	30	CLL	HD	Postmortem
9	Keiser et al.[13]	1961	M	59	CLL	HD	Antemortem
10	Keiser et al.[13]	1961	M	64	CLL	HD	Postmortem
11	Lortholary et al.[15]	1964	M	51	CLL	HD	Postmortom
12	Lortholary et al.[15]	1964	M	58	CLL	HD	Antemortem
13	Lortholary et al.[15]	1964	F	60	CLL	HD	Postmortem
14	Oberfield[19]	1966	F	55	CLL	HD	Postmortem
15	New Eng. J. Med.[2]	1966	F	39	CLL	HD	Antemortem
16	Tornyos et al.[24]	1967	M	67	CLL	HD	Postmortem
17	Orts & Manez[20]	1967	M	50	CLL	HD	Antemortem

lymphocytic leukemia. This patient died 2 years after the time of diagnosis. At autopsy, the diagnosis of Hodgkin's disease was confirmed; lymphocytic infiltration suggestive of lymphocytic leukemia was found in the lymph nodes, spleen, liver, and bone marrow. This case does not meet generally accepted criteria for chronic lymphocytic leukemia. Our case seems to be unique, with classical chronic lymphocytic leukemia developing during a prolonged remission of Hodgkin's disease.

An occurrence of myeloid leukemia in 3 patients with Hodgkin's disease was recently reported by Ezdinli et al.[4] from our Institute. The only common factor in these 3 patients and 4 of 5 cases with coexistent Hodgkin's disease and myeloid leukemia reported by others was radiation therapy. These authors concluded that these cases probably represent radiation-induced leukemia. This conclusion was strengthened by the incidence of leukemia in Hiroshima atomic bomb survivors.[10] Chronic myelocytic leukemia was commonly observed among those of middle age, in both the heavily and lightly exposed group. However, acute leukemia predominated among those who were under 9 years of age or over 60 in the heavily exposed group. It is of interest that no case of chronic lymphocytic leukemia was encountered among atomic bomb survivors. Although our patient received irradiation 13 years prior to the diagnosis of chronic lymphocytic leukemia, we feel that the radiation was not an inducer of this leukemia and that these two diseases were merely coincidental in the same patient.

The etiologic interrelationship among Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, and chronic lymphocytic leukemia is not well defined. It is generally agreed that lymphosarcoma may at times transform into either chronic lymphocytic leukemia or

TABLE 3. Summary of Our Case and Reported Cases with Hodgkin's Disease (HD) Complicated by Chronic Lymphocytic Leukemia (CLL)

Case no.	Authors	Year	Sex	Age	Primary diagnosis	Secondary diagnosis	Time of secondary diagnosis
1	Warthin[25]	1906	F	45	HD	CLL	Antemortem
2	Watson[27]	1938	M	65	HD	CLL	Postmortem
3	Present case	1970	M	35	HD	CLL	Antemortem

reticulum cell sarcoma, and Hodgkin's disease may transform into reticulum cell sarcoma in the course of the disease. Richter[22] first reported a case of chronic lymphocytic leukemia complicated by reticulum cell sarcoma. Since then, more cases of such association of these two diseases have been reported.[6] Conversion of reticulum cell sarcoma from chronic lymphocytic leukemia seems to be a usual progression of the disease.

The relationship between Hodgkin's disease and lymphosarcoma or chronic lymphocytic leukemia is uncertain. Hodgkin's disease and other malignant lymphoproliferative disease are usually regarded as distinct neoplastic entities. In addition to unusual cases of association of Hodgkin's disease and chronic lymphocytic leukemia already mentioned, there were a few reports[9,26] describing an association of Hodgkin's disease and lymphosarcoma in the same individual. This association of Hodgkin's disease and chronic lymphocytic leukemia in our case probably represents the occurrence of two separate diseases, although the possibility that Hodgkin's disease can transform into chronic lymphocytic leukemia is not entirely ruled out.

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