Panctytopenia and Leukemia in Hodgkin’s Disease: Report of Three Cases

By P. L. Weiden, K. G. Lerner, A. Gerdes, J. D. Heywood, A. Fefer, and E. D. Thomas

Three patients with Hodgkin’s disease who developed severe pancytopenia terminating in acute leukemia (two patients) or preleukemia (one patient) are presented. Prior treatment consisted of radiation therapy alone in two patients, and radiation plus chemotherapy in the third. The only patient in whom chromosomal analysis was performed showed an abnormal chromosome. Therapeutic radiation exposure is thought to contribute to the development of leukemia in such patients.

Leukemia is an uncommon complication of Hodgkin’s disease, but is being reported with increasing frequency. The rapid evolution of more aggressive modes of therapy makes it imperative that we seek more information regarding the incidence of this complication in order to achieve maximum therapeutic benefit for patients with Hodgkin’s disease.

FEWER THAN 35 patients with Hodgkin’s disease have been reported to develop acute leukemia.1 4 Although this has been considered to be a relatively rare occurrence, approximately half of the cases have been reported within the past 4 yr. We have recently encountered three additional patients with Hodgkin’s disease who developed acute leukemia within a single year. In each of our patients, prolonged pancytopenia developed following appropriate therapy (radiotherapy alone in two cases) and ultimately terminated in acute leukemia in two patients and “preleukemia” in the third. Because of the tendency toward more aggressive radiotherapy and chemotherapy in the treatment of Hodgkin’s disease, constant reevaluation of the possible risks associated with such therapy is indicated. For this reason, the following three cases are reported.
CASE REPORTS

Patients were evaluated and treated at several teaching hospitals affiliated with the University of Washington School of Medicine. All pathological material has been reviewed and diagnoses revised according to currently accepted criteria. Radiation therapy was administered using 60Co unless otherwise specified.

Case I

A 51-yr-old white male was found to have Hodgkin's disease, clinical stage IIIA, nodular sclerosis type, in May 1968. All routine laboratory tests were within normal limits. The platelet count was 185,000/cu mm, and marrow aspirate was normal with slightly increased number of megakaryocytes. He received mantle field irradiation, tumor dose of 3900 rads in 43 days, followed by paravertebral pelvic irradiation, 4450 rads tumor dose in 76 days. The latter course was interrupted midway for 1 mo because of the development of thrombocytopenia (nadir 16,000/cu mm). Marrow suppression was evident following completion of radiotherapy (hematocrit 28%, WBC 2500-4000/cu mm and platelets 15,000-30,000/cu mm). The hematocrit returned to normal after 15 mo and the white count to normal after 12 mo, but minimal thrombocytopenia (140,000/cu mm) persisted.

He was presented again in September 1971 with progressive fatigue without symptoms or signs attributable to Hodgkin's disease. Pancytopenia was documented with hematocrit 16%, total white blood count 1300-2600/cu mm, absolute granulocyte count 350-600/cu mm and platelet count 18,000-30,000/cu mm. Uncorrected reticulocyte count was 4.2%. Radiographic studies including lymphangiogram and scans of liver, spleen, and bone revealed no evidence of active disease. Marrow scan showed an expanded marrow space. Marrow aspirate and biopsy demonstrated decreased cellularity with markedly decreased megakaryocytes, occasional normoblasts with nuclear maturation defects, and poor maturation sequence of the myeloid series with the predominant cell being the myeloblast. Chromosomal analysis revealed a partial deletion of the long arm of one of the D group chromosomes in four of 28 bone marrow cells examined. Coomb's test was weakly positive with 329 molecules of gamma globulin per red blood cell. The patient was treated with prednisone, 60-100 mg, and oxymethalone, 150-200 mg, daily.

Over the next 3 mo, he required 6 U of red blood cells and remained stable with persistent fatigue and intermittent low-grade fever. Peripheral counts showed no response to the steroid regimen; marrow examinations in October and November showed no significant change. In late December, fever to 103°F and nonspecific symptoms marked emergence of a frankly leukemic state, with 1900 myeloblasts/cu mm in the peripheral blood. Marrow aspirate and biopsy showed focal areas of hypercellularity with 80% myeloblasts. Many of these were morphologically abnormal with large nuclei; prominent nucleoli; and basophilic, often vacuolated, cytoplasm containing reddish granules but no distinct Auer rods (Fig. 1). Karyotype at this time demonstrated the abnormal chromosome to be present in 17 of 19 cells examined.

Subsequently, the patient was treated with high-dose cyclophosphamide (200 mg/kg) and marrow transplantation from a genotypically matched sibling, but succumbed 17 days later with intracranial hemorrhage. At autopsy, there was no evidence of Hodgkin's disease or leukemia.

Case II

In 1963 clinical stage IIA Hodgkin's disease, nodular sclerosis type, was diagnosed in this 16-yr-old white male. Orthovoltage radiation therapy of 3200 R in air to mediastinal and left
cervical ports was administered. He subsequently received chlorambucil and vincristine until May 1968 when paraortic disease was demonstrated by lymphangiogram. This was treated with 3500 rads 60Co irradiation to a standard paravertebral-pelvic field. Radiation was well tolerated with leukocyte nadir of 3700/cu mm and platelet nadir of 44,000/cu mm midway through treatment. During the next 2.5 yr the patient was treated with alkylating agents, vinca alkaloids, procarbazine, and steroids. Marrow examinations were initially within normal limits, but, in retrospect, occasional (<1%) immature mononuclear cells characterized by large nuclei with nuclear folding and lobulation, intermediate chromatin clumping, and rare cytoplasmic granules were present intermittently beginning in 1965 (Fig. 2A).

In January 1971, the patient developed pneumococcal pneumonia at which time pancytopenia was recognized: hematocrit 11.5%, white blood cells, 1060–3400/cu mm with absolute granulocyte counts 50–1800/cu mm, and platelets 41,000–62,000/cu mm. Reticulocyte count was 1.0%–1.5% uncorrected. Peripheral smear showed moderate poikilocytosis, occasional plasma cells, and young, atypical lymphocytes. Marrow aspirate showed normal cellularity, mildly megaloblastic erythropoiesis, left-shifted myelopoiesis and more frequent atypical, "myelomonocytoid" cells. Serum folate, vitamin B12, haptoglobin, and Coomb's test were normal. Pancytopenia and infection persisted as major clinical problems; in March marrow examination was essentially unchanged. The patient appeared to stabilize with minimal improvement in peripheral counts until November 1971, when symptoms attributable to hematocrit of 11% developed. Leukocyte count was 800/cu mm with 50 granulocytes/cu mm and platelet count was 7000/cu mm. Occasional blast cells were seen in the peripheral blood, and the marrow contained approximately 80% atypical myelomonoblasts with only occasional nucleoli, nuclear folding, cytoplasmic vacuoles, and azurophilic cytoplasmic granules (Fig. 2B). The patient expired several days later of intracranial hemorrhage.

At postmortem generalized lymphadenopathy was present, and a 5-cm mass enveloped the abdominal aorta. Sections of this mass revealed only dense connective tissue and those of the lymph nodes showed an immunoblastic reaction with no evidence of Hodgkin's disease. The lumbar marrow showed patchy fibrosis surrounding islands of lymphocytes, plasma cells, and atypical histiocytes, many of which resembled degenerating Reed-Sternberg cells. In contrast, the sternal and iliac marrow showed monotonous proliferation of blast-type cells compatible with acute leukemia. Thus, early acute leukemia and evidence of residual Hodgkin's disease were found.

Case III

Hodgkin’s disease, clinical and pathological Stage IIIB, mixed cellularity type, was diagnosed in May 1970 when this white male was 26 yr old. Initial hematocrit was 35.5%, leukocyte count 10,100/cu mm, and platelets were increased on smear. Total nodal irradiation was undertaken from June to November 1970: 4300 rads tumor dose to mantle field, 3950 rads to paravertebral–splenic field, and 4000 rads to pelvic-inguinal field. The pelvic irradiation was interrupted midway for 3 wk because of thrombocytopenia (nadir 55,000/cu mm) and leukopenia (nadir

Fig. 2. Bone marrow aspirates from Case II. Wright’s-Giemsa stain. (A) Immature mononuclear cells in examination of September 1965; original magnification 1000x. (B) Leukemic blast cells in examination of November 1971; original magnification 630x.
Fig. 3. Case III: needle bone marrow biopsy from lateral iliac crest obtained March 1972. Hemotoxylin and eosin stain. (A) Original magnification 100x. Note clusters of two types of mononuclear cells and background of moderate fibrosis. (B) Higher power view (original magnification 400x) of immature mononuclear cells.

3100/cu mm). His leucocyte count and hematocrit rose to normal 1 mo and 5 mo following completion of therapy, respectively. After 5 mo, however, the platelet count was only 132,000/cu mm and subsequently fell.

In October 1971 the patient was admitted with easy bruising and epistaxis attributable to a platelet count of 10,000 15,000/cu mm. Hematocrit was 31.2%, with reticulocyte count 3.7%. Leukocyte count was 6400/cu mm with 81% polymorphonuclear cells; a single blast cell was seen on scanning several smears. Marrow aspirations and biopsies twice revealed markedly decreased megakaryocytes, occasional normoblasts with nuclear maturation defects, slightly left-shifted myelopoiesis, and occasional (1%, 2%) atypical myelomonocytic cells with large irregular nucleoli and folded nuclear margins.

The patient stabilized without therapy and for the next 4 mo his hematocrit was 24%, 28%, white blood count 4500-9600/cu mm and platelet count 24,000-42,000/cu mm. In early March 1972, however, his hematocrit fell to 18%, and subsequently he required red cell transfusions. Except for a transient decrease to 11,000/cu mm, his platelet count remained 28,000-34,000/cu mm, while granulocyte counts remained normal. Multiple attempts to aspirate marrow from the lateral posterior and anterior iliac crest (i.e., outside the radiation fields) were now unsuccessful, but two separate needle biopsy specimens were obtained (Figs. 3A and 3B). Touch preparations revealed poor myeloid maturation and more frequent atypical, "myelomonoblastic" cells.

On routine histologic sections decreased numbers of normal marrow elements and 2+ reticulin fibrosis were seen. In addition, focal collections of two cell types were evident: the first, mature lymphocytes, and the second, less mature cells with angular nuclear margins, prominent nucleoli, and relatively prominent cytoplasm. Although these could not be identified conclusively, their focal occurrence as collections of monotonous immature cells was suggestive of a leukemic process, particularly when evaluated with the touch preparations. The patient was discharged on oxymethalone and 2 wk later his hematocrit was 12%, and granulocyte count 1000/cu mm. He was admitted to another hospital for blood transfusion, and unexpectedly expired. A gross postmortem examination revealed bilateral pneumonia, but material was not available for histological examination.

DISCUSSION

Chan and McBride have recently summarized the reports of cases of leukemia, excluding cases of chronic lymphocytic leukemia, in patients with Hodgkin's disease. Three additional case reports have subsequently appeared. Of 34 patients, the majority developed variants of acute myeloid or undifferentiated leukemia, as was true in at least two of our cases. Also, an interval of more than 5 yr between diagnosis of Hodgkin's disease and development of leukemia was present in more than half of the patients, and many were
Table 1. Summary of Case Reports *

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Radiation Fields</th>
<th>Chemotherapy</th>
<th>Interval From Diagnosis of Hodgkin's Disease to Diagnosis of Leukemia</th>
<th>Interval From Last Therapy to Recognition of Pancytopenia</th>
<th>Interval From Recognition of Pancytopenia to Diagnosis of Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>51</td>
<td>M</td>
<td>Mantle, paravertebral-pelvic</td>
<td>None</td>
<td>3 yr 7 mo</td>
<td>2 yr 11 mo</td>
<td>3 mo</td>
</tr>
<tr>
<td>II</td>
<td>23</td>
<td>M</td>
<td>Mediastinal, left cervical, paravertebral-pelvic</td>
<td>Multiple drugs</td>
<td>7 yr 11 mo</td>
<td>1 mo</td>
<td>11 mo</td>
</tr>
<tr>
<td>III</td>
<td>28</td>
<td>M</td>
<td>Total nodal</td>
<td>None</td>
<td>1 yr 10 mot</td>
<td>11 mo</td>
<td>4 mot</td>
</tr>
</tbody>
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* For details, refer to text.
† Diagnosis based on marrow biopsy (see text).
‡ Granulocytes within normal limits until 5 mo later.

apparently free of Hodgkin's disease at the time they developed leukemia. Each of our patients can be characterized as having had a period of clinically significant pancytopenia with marrow atypicality prior to the development of a frankly leukemic state (Table 1). Although pancytopenia was thus a prominent feature in each of our cases, this is an infrequent mode of presentation of leukemia in Hodgkin's disease. In fact, only one of the patients previously reported presented with pancytopenia. On the other hand, in other settings, leukemia not uncommonly is preceded by pancytopenia and/or an " aplastic" marrow. This appears to be true whether the initial marrow damage is spontaneous or the result of a known toxic insult. Dameshek has previously suggested that leukemia may develop from the proliferation of an abnormal clone of leukocytes during the attempt of a hypoplastic marrow to repair itself. The marked increase during a 3-mo period in the proportion of marrow cells containing the same abnormal chromosome in Case I would be consistent with this hypothesis.

The incidence of leukemia in Hodgkin's disease is difficult to establish from the several case reports available in the literature, but would nevertheless appear to be low. On the other hand, the three cases reported here were all cared for at the affiliated hospitals of the University of Washington, where an average of 25 newly diagnosed patients with Hodgkin's disease have been treated during each of the past 5 yr. During the past 12 yr, approximately 160 patients have received radiotherapy for Hodgkin's disease at our institution. Thus, it would appear that an incidence of leukemia as high as 2% might exist in this group of retrospectively surveyed patients with Hodgkin's disease.

Patients with Hodgkin's disease may develop other nonlymphomatous malignant tumors as well as leukemia. Arseneau et al. have recently reviewed the experience at the National Cancer Institute, particularly with reference to the possible influence of intensive therapy on the development of second malignancies. They found a significantly increased incidence of second tumors in those patients treated with intensive radiotherapy, and an especially significant increased incidence in a group of 35 patients treated with both intensive radiotherapy and intensive chemotherapy. Chemotherapy, altered host immune
status, and radiotherapy have all been suggested as factors contributing to the development of leukemia and other malignancies in Hodgkin's disease. The role of each has been difficult to evaluate, but, as additional cases occur, it may be possible to assess the relative importance of these and other factors. For example, two of the cases reported here (Cases I and III) never received chemotherapeutic agents. This does not, of course, exclude the possibility that these drugs, either because of their marrow suppressive or immunosuppressive effects, might be a contributing factor in some cases, but it does suggest that they are not a necessary factor.

Hodgkin's disease has long been associated with depression of cellular immunity. Recently, however, Young et al. have shown that cutaneous anergy is actually relatively uncommon in Hodgkin's disease, and that skin reactivity, if initially absent, usually returns when the disease is in complete remission. Alterations of cellular immunity have been associated with the development of malignancy in animal models and in patients with congenital or acquired immune deficiency syndromes, or those receiving chronic immunosuppression following transplantation. In most instances, however, these neoplasms are of the lymphoreticular system rather than leukemias. Any deficiency of the immune system which may exist in Hodgkin's disease would hence seem unlikely to account for the observed development of predominantly myeloid leukemias.

Radiation exposure has been implicated in the subsequent development of leukemia in a variety of circumstances. Individuals exposed to radiation for treatment of ankylosing spondylitis or during the Japanese atomic bomb explosions, early American radiologists, and children irradiated for an enlarged thymus or in utero all show significantly increased incidences of leukemia compared to appropriate control groups. On the other hand, a carefully done, prospective study of patients exposed to radiotherapy for cervical cancer failed to demonstrate any increase in the incidence of leukemia. Most patients with Hodgkin's disease during the past two or three decades have received radiotherapy at some time, so that it is not possible to compare the incidence of leukemia in patients exposed and not exposed to therapeutic radiation. All reported patients with Hodgkin's disease who have developed leukemia have had prior radiotherapy, albeit in some instances seemingly minimal doses. Certainly many patients with Hodgkin's disease have received extensive radiotherapy, especially during the past decade, and the incidence of leukemia remains low.

Furthermore, although some marrow suppression during and after radiotherapy is not uncommon, most patients recover adequate marrow function and are usually able to tolerate subsequent chemotherapy. Each of our patients experienced moderate marrow suppression during his radiotherapy, and in two this was severe enough to require temporary interruption of the planned therapy schedule. This toxicity was not excessive in view of the extended fields employed, and by itself does not serve to distinguish these patients from others similarly treated. In fact, nothing in the early clinical course of our patients or those in the literature allows one, even in retrospect, to predict the development of late pancytopenia and/or leukemia.

Nevertheless, it remains most likely that therapeutic radiation exposure does contribute to the development of leukemia in patients with Hodgkin's disease.
Others have concluded that this increased risk of leukemia is still small and certainly justified in view of the significant therapeutic benefit that has accompanied more aggressive radiotherapy.21 We do not disagree with this contention. We only wish to urge that as more patients receive more radiotherapy and survive longer, attempts should be made to define and follow the incidence of leukemia and other malignancies as a late complication of Hodgkin’s disease. Recognition of a significant incidence of late malignancies in patients treated with aggressive radiotherapy would justify continued efforts to find an even better form of treatment for Hodgkin’s disease.

ACKNOWLEDGMENT

We thank Robert Ramberg for performing the chromosomal analyses.

REFERENCES

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