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Hodgkin's Disease of the Bone Marrow[1]

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Summary

The identification of Hodgkin's disease involving the bone marrow is possible with needle and/or open biopsy techniques. Despite the small fraction of marrow sampled by these techniques, the yield of positive biopsies is 9% in previously untreated patients whose disease is more advanced than Stage II. There is a tendency for marrow involvement to be identified in male, older patients with systemic symptoms and an elevated serum alkaline phosphatase. It is unusual for marrow involvement to result in significant blood count depressions, especially in untreated patients. No involvement of other extranodal sites of disease was identified in nearly one-half of the patients and as such this has important therapeutic implications. The prognostic significance of marrow involvement is not hopeless. Under cyclical combination chemotherapy with nitrogen mustard; vincristine, procarbazine, and prednisone, the actuarial survival at 2 years is 84%, although only 21% of the patients are free of disease 18 months after treatment initiation.

The biopsy procedures are recommended for all patients at onset with Stage III extent or greater and is desirable for all patients with systemic symptoms. It is also recommended for all patients who have developed recurrence of disease or symptoms, elevation of the serum alkaline phosphatase, or unexplained blood count depressions after radiotherapy.

Introduction

The identification of Hodgkin's disease involvement of the bone marrow has become of increased importance as radical radiotherapy approaches have been developed for patients with more advanced stages of the disease. An accurate assessment of bone marrow involvement had not been possible before the routine utilization of biopsy techniques in patients' initial evaluation and subsequent management (4, 8). A group of 36 patients with documented Hodgkin's disease of the bone marrow has been analyzed, 16 occurring during the initial evaluation of previously untreated patients and 20 occurring later in the course of the disease. The clinical and laboratory setting for Hodgkin's disease of the bone marrow is presented. The prognostic significance of this occurrence and the response of these patients to palliative and combination chemotherapy is reviewed.

Materials and Methods

The clinical and laboratory features of all patients at Stanford University Medical Center who have had a bone marrow interpreted as positive for Hodgkin's disease as part of previously published protocol studies were reviewed. Patients not included in the protocol studies but whose bone marrow was interpreted as positive by the Surgical Pathology Department since January 1, 1969, and all patients known to me and cared for by the Medical Oncology and Radiotherapy Division since 1961 were reviewed. Of 40 patients so identified, adequate clinical data for analysis at the time of the positive bone marrow were available in 36 patients.

The histopathological criteria for Hodgkin's disease involvement of the bone marrow requires comment. In 29 of these patients, all of the features of Hodgkin's disease were present with identified Reed-Sternberg multinucleated giant cells in an appropriate pleomorphic cellular stroma (5, 6). Seven patients had abnormal marrow infiltration with an admixture of lymphocytes, histiocytes, and various degrees of fibrosis, replacing the normal marrow, but without identifiable classical Reed-Sternberg cells. In patients with documented Hodgkin's disease in other sites, we have accepted this pathological picture as representing Hodgkin's disease in the bone marrow. The clinical features of these 7 patients are no different than those of the other 29 patients and are included in this review. Presumably, if more pathological material were available for study, typical Reed-Sternberg cells would be discovered in these cases since it is not unusual for pathologists to spend prolonged periods surveying serial sections of otherwise typical tissue to identify the diagnostic Reed-Sternberg cell.

The usual diagnostic approach for bone marrow evaluation for patients with Hodgkin's disease has been to obtain a bone marrow aspirate from the region of the posterior-superior iliac spine and prepare coverglass smears. A portion of the aspirate is fixed in formalin, and hematoxylin and eosin-stained sections are prepared. At the same time, a Westerman-Jensen needle biopsy is obtained from the same general location and processed by the Surgical Pathology division. If these studies are negative for Hodgkin's disease involvement, and there are no other contraindications for exploratory laparotomy and splenectomy, an open Stryker drill biopsy core is obtained from the anterior iliac crest at the time of exploratory surgery (3). These specimens, approximately 1 cm in diameter, are shaved of their cortical bone, decalcified and prepared for sectioning. Although this routine has been our protocol approach, the sequence has not been adhered to for nonprotocol patients; and frequently the Westerman-Jensen needle biopsy has been omitted by our resident staff when they felt patients would be undergoing open biopsy under general anesthesia.

The clinical records of 60 consecutive Hodgkin's disease protocol patients evaluated during 1970 were used to provide control information about laboratory findings in patients with

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negative bone marrow studies. The control patients all had negative open marrow biopsies for Hodgkin's disease.

Patients have been staged using the Rye-Paris classification (7, 11) after extensive diagnostic studies, previously described (9, 10).

Although bone marrow study is routine for all previously untreated patients with Hodgkin's disease at Stanford Medical Center, this is not so for patients who have developed recurrences or extension of their disease to sites beyond radiotherapy control. Those patients identified later in their course to have Hodgkin's disease of the bone marrow are a selected group, in which the marrow may be the only known site of disease, or the only Stage IV site. It is very likely that many more patients would have demonstrable random marrow involvement by the biopsy techniques, if patients late in their course, or with widespread pulmonary, hepatic or osseous involvement were studied routinely and at intervals.

Results

Table 1 shows the technique utilized for the demonstration of Hodgkin's disease in the marrow. In one instance, the hematoxylin-eosin section of the aspirated marrow provided diagnostic material. In 12 patients Westerman-Jensen needle biopsies were positive; 7 of these 12 had negative aspirates. No open biopsies were performed in these 12 patients. In 23 patients the open technique was positive. Sixteen of these 23 had negative aspirates, and eight had negative needle biopsies. Of the 36 with biopsy material which was positive, seven had aspirations performed which are considered "inadequate" for interpretation or categorized as a "dry tap."

Of 155 consecutive untreated patients admitted for protocol study of Hodgkin's disease, 8 or 5% had a positive bone marrow. These 8 patients were all within a group of 88 patients who had Stage III disease or more (other than their marrow involvement), an incidence of 9%, in previously untreated patients with more advanced disease.

Of the 36 patients, 24 were male. Of 32 who had their initial lymph node disease classified by the Rye classification, 17 had nodular sclerosis, 13 had mixed cellularity, 1 had lymphocyte predominance, and 1 had lymphocyte depletion. The histopathological distribution of all patients seen at Stanford includes approximately 75% with the nodular sclerosis type, 13% with mixed cellularity, 10% with lymphocyte predominance, and 2% with lymphocyte depletion (R. Dorfman, personal communication). The patients with the mixed-cellularity type appear to have a somewhat greater incidence of marrow involvement, although the numbers are small.

The median age of the 16 patients with bone marrow involvement at onset was 48 years (range, 17 to 72), which is significantly older than the general Hodgkin's disease population seen at Stanford. Fourteen of the 16 had systemic symptoms. Of the 20 patients who develop marrow involvement later in their course, the median age was 28 years (range, 3 to 65). Systemic symptoms were present in 17 of 20 at the time of later marrow involvement.

Seven of the 16 patients, positive at onset, had disease in other extranodal sites (3 in bone, 2 in liver, 1 in lung, and 1 in both lung and bone). Of 20 patients with a positive bone marrow during the course of the disease, 18 had complete clinical evaluation and 12 of these 18 had other extranodal sites of disease (3 in bone, 7 in liver, 1 in lung, and 1 in both lung and pleura). Thus, in 15 patients the bone marrow involvement was the only known site of extranodal disease.

In these 36 patients, 15 had documented involvement of the spleen (8 concurrently and 7 earlier in their course) and 9 had presumptive involvement of the spleen based upon splenic enlargement. Ten patients were presumed to have no splenic involvement because of its normal size, clinically. Two patients had uninvolved spleens at laparotomy, 6 and 12 months earlier. No patient has had a documented normal spleen, verified at splenectomy, at the time a positive marrow was discovered.

Laboratory Findings

Charts 1 and 2 compare the routine blood counts and serum alkaline phosphatase in the patients with marrow involvement and the 60 consecutive patients without identified marrow involvement. Most patients with marrow involvement had peripheral blood counts within the same range as the control group, many of them having normal values. However, in the untreated patients, a white blood cell count below 5,000, platelet count below 150,000, or hematocrit below 29% was not seen unless there was bone marrow involvement or obvious hypersplenism.

The serum alkaline phosphatase was of the greatest predictive value in identifying patients with Hodgkin's disease of the bone marrow. Only 4 of 34 patients with recorded values at the appropriate time had levels within the normal range. Two others, ages 11 and 15, had elevations within the range acceptable for the growth period. In the control group without marrow involvement, 18 of 60 patients had alkaline

Table 1

Hodgkin's disease of the bone marrow

Seven aspirates were considered "inadequate" or "dry taps."

Technique	No. positive	
Aspiration	1	(Section of clot)
Westerman-Jensen needle biopsy	12	Aspirate ⊖ in 7
Open biopsy	23	Aspirate ⊖ in 16 Westerman-Jensen needle ⊖ in 5 Westerman-Jensen needle ⊕ in 3

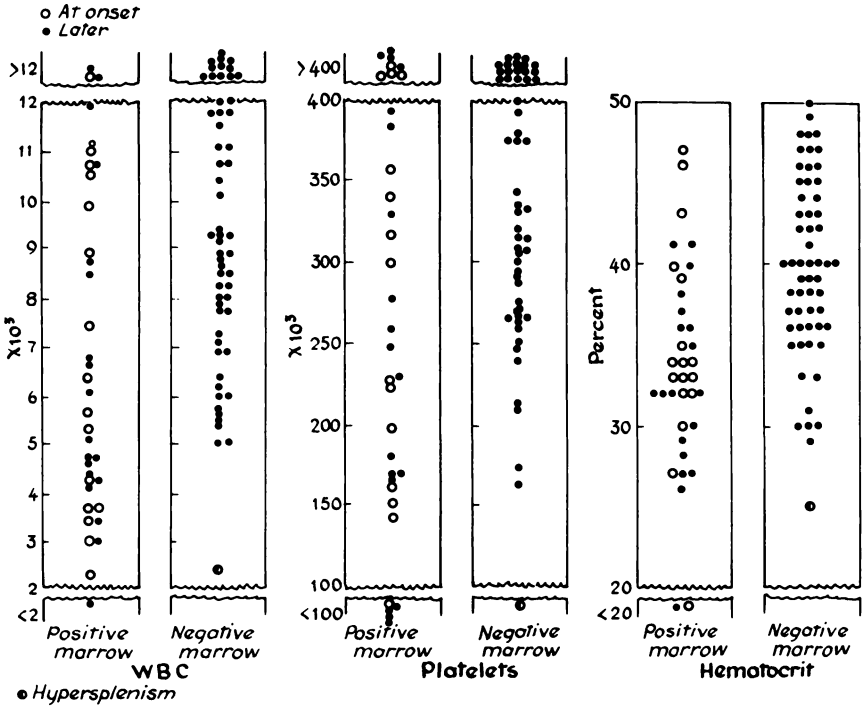

Chart 1. Peripheral blood counts of 36 patients with Hodgkin's disease of the bone marrow, compared to 60 patients without bone marrow involvement.

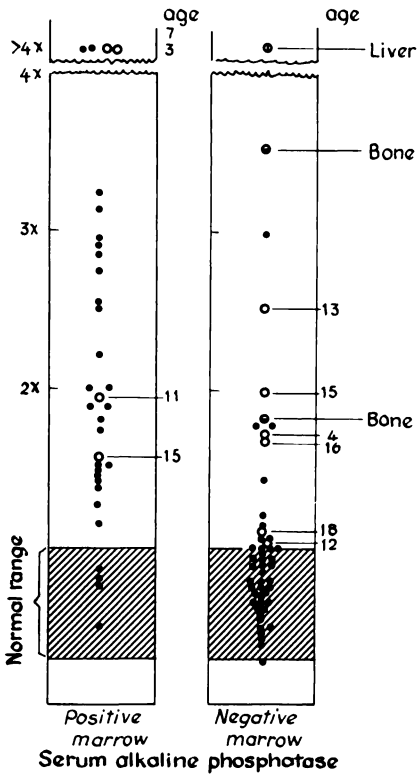

Chart 2. Serum alkaline phosphatase levels of 36 patients with Hodgkin's disease of the bone marrow, compared to 60 patients without bone marrow involvement. (*2x*, *3x*, and *4x*, 2, 3, or 4 times the upper limit of normal for the different methods and units used). Age is in years.

phosphatase elevations; 6 could be explained by the age of the patient and 3 by documented involvement of liver or bone. Five others were borderline elevations. The 4 remaining patients had levels 1.5 to 3 times the upper limit of normal and are not explained. The patients with the highest elevation, 250 i.u. (normal range, 30 to 85 i.u.) and who had otherwise Stage $III_S A$ disease, had a return toward normal following total lymphoid radiation, to a level of 110 i.u., and a level of 88 i.u. after 2 of 6 planned cycles of MOPP,[2] combination chemotherapy (2) as part of her treatment protocol.

Prognostic Significance

The prognostic significance of bone marrow involvement identified by a routine random biopsy technique has not been known. Experienced clinicians have the opinion that severe anemia or pancytopenia as a result of marrow replacement is a grave prognostic sign. Bone marrow involvement, unassociated with significant blood count depressions, had not been sought or identified in former studies.

The survival of these patients has been analyzed by the method of Berkson and Gage (1). Chart 3 shows the survival curves of all the patients from the time of diagnosis in those with marrow involvement at the onset and from the time of identification of marrow involvement in those who developed this extension later in their course. In the former group, the 2-year survival is 70%; in the latter it is 46%. These figures do not differ significantly for the number of patients involved.

[2] The abbreviation used is: MOPP, a cyclic chemotherapy program utilizing nitrogen mustard, vincristine, procarbazine, and prednisone.

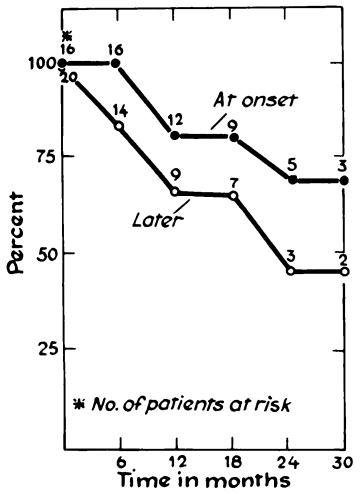

Chart 3. Actuarial survival (Berkson-Gage) for patients with Hodgkin's disease of the bone marrow from the date of diagnosis, if discovered at onset, or from the date of marrow involvement, if discovered later in the course.

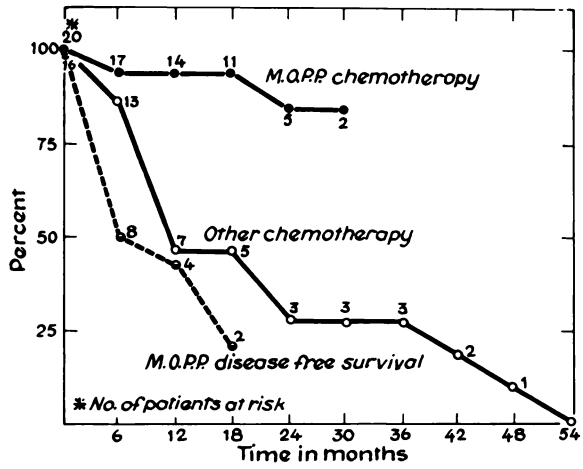

Chart 4. Actuarial survival (Berkson-Gage) for patients with Hodgkin's disease of the bone marrow comparing palliative and aggressive (MOPP) chemotherapy approaches.

The therapeutic approach to patients with advanced Hodgkin's disease has changed in the last 5 years, stimulated by the very good results reported by DeVita *et al.* (2) for combination chemotherapy. Chart 4 shows the survival curves for patients with bone marrow involvement, whether at the onset of their disease or later in their course, who have been treated with the MOPP combination chemotherapy and those treated with single-drug palliative approaches. The survival curves are significantly different, with a 2-year survival of 84% for those treated with MOPP and 28% survival at 2 years for those treated otherwise.

It appears, therefore, that the use of aggressive chemotherapy has improved survival for patients with advanced disease. There are several reservations, however, which qualify the enthusiasm for the combination chemotherapy approach. As shown in Chart 4, despite the good survival of patients receiving MOPP, one-half of the patients have relapsed within 6 months, usually during their chemotherapy attempts. Although the number of patients is very small, the 18-month disease-free survival is only 21%. After relapse, or failure to control disease activity with MOPP, conventional chemotherapy utilizing Velban, local irradiation, or no therapy for asymptomatic patients has been the therapeutic approach.

Another difficulty in comparing these 2 therapeutic approaches results from the different periods during which patients were seen in each group. All patients except one who have been seen in the last 3 years have received MOPP. During this 3-year period the Stanford protocol studies have included patients with bone marrow involvement. Whether this has resulted in a hidden favorable factor of case selection or provided some other advantages in terms of overall management is not known. Only if a randomized study comparing the different therapeutic approaches had been carried out could a firm conclusion favoring the MOPP program be made.

Despite these reservations, it does appear that early aggressive combination chemotherapy of the MOPP type provides an advantage in terms of survival for patients with Hodgkin's disease of the bone marrow, despite relapse in the majority of patients. These observations have implications to the design of therapeutic studies for the better management of all patients with Hodgkin's disease.

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