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BONE MARROW INVOLVEMENT IN THE NON-HODGKIN'S LYMPHOMATA

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Summary.—The frequency, clinical settings and histopathological correlations of bone marrow involvement in the non-Hodgkin's group of malignant lymphomata is presented. The importance of formal bone marrow biopsy is stressed. The overall frequency of involvement in a prospectively studied group of 109 patients is 41%. In one subgroup, those with nodular lymphocytic poorly differentiated lymphoma, the incidence is 85% in previously untreated patients.

IN A PREVIOUS report from Stanford, the frequency and clinical features of bone marrow involvement in patients with malignant lymphoma other than Hodgkin's disease were analysed (Jones, Rosenberg and Kaplan, 1972). In that retrospective review important correlations of the incidence of bone marrow involvement with the various subgroups of the Rappaport (Rappaport, 1966) classification were made. Among previously untreated patients who had bone marrow examination by any technique, the frequency of involvement varied between 5% and 30% within the subgroups. In this report, a prospective series of 109 patients has been studied routinely with bone marrow biopsy. Similar correlations are made. The overall frequency of bone marrow involvement is higher, 41% compared with 16·5% of the retrospective series. In one subtype, the nodular lymphocytic poorly differentiated group, 28 of 33 previously untreated patients, or 85%, had identifiable involvement of the bone marrow at the time of presentation. The clinical features of these patients are described.

PATIENT SELECTION AND METHODS

A consecutive series of 109 previously untreated patients was studied as part of a prospective therapeutic trial which was initiated in July 1971. The following criteria were required for patient eligibility: (1) Age between 10 and 70 years, inclusive; (2) patient's usual place of residence was within 300 miles of Stanford Medical Center; (3) no serious, unrelated medical condition was known which would preclude the use of diagnostic studies, including lymphography, exploratory laparotomy with splenectomy or the use of aggressive irradiation and/or chemotherapy programmes; (4) agreement by the patients and referring physician to participate in a randomized clinical trial testing several alternative therapy programmes.

Patients must have had satisfactory biopsy material reviewed by the Division of Surgical Pathology at Stanford and classified utilizing the criteria of Rappaport (Rappaport, 1966). The histological subgroups which were used are shown in Table I.

The details and criteria for identification of bone marrow involvement were those of Dorfman and his colleagues and are presented elsewhere in this Symposium (Dorfman and Kim, 1975). Cytological features of lymphoid malignancy were required to distinguish involvement from the lymphoid nodules which are present in the bone marrow of normal individuals.

Relatively arbitrary criteria were used to distinguish patients with chronic lymphocytic leukaemia from patients with lymphoma. Patients were excluded from

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TABLE I.—*Non-Hodgkin's Lymphomata, Histopathological Types (Rappaport, 1966)*

Nodular	Diffuse
Nodular histiocytic (NH)	Diffuse histiocytic (DH)
Nodular mixed histiocytic-lymphocytic (NM)	Diffuse mixed histiocytic-lymphocytic (DM)
Nodular lymphocytic poorly differentiated (NLPD)	Diffuse lymphocytic poorly differentiated (DLPD)
Nodular lymphocytic well differentiated (NLWD)	Diffuse lymphocytic well differentiated (DLWD)
	Diffuse undifferentiated (DU)

this study and the therapeutic trials if all 3 of the following features were present: (1) Lymph node histology was of the diffuse, lymphocytic well differentiated type; (2) peripheral lymphocytosis was 4000 or more per mm^3; (3) bone marrow was diffusely infiltrated with well differentiated lymphocytes.

Though these criteria were developed for the anticipated difficulty in making the distinction between patients presenting with chronic lymphocytic leukaemia who may have had a lymph node biopsy, no patient referred to the Division of Medical Oncology or the Division of Radiation Therapy fulfilled these criteria.

Bone marrow biopsy and aspiration were performed on most patients on their first clinical visit. Either a Westerman-Jensen or Jamshidi needle was used, the specimen obtained from the region of the posterior-superior iliac spine. Complete blood counts, blood chemistry, chest x-rays and bipedal lymphography were obtained in all cases.

Initially a group of 8 patients was taken to exploratory laparotomy despite a positive bone marrow examination. Thereafter, only patients in whom the marrow biopsy was negative, equivocal or not obtained were subjected to diagnostic laparotomy. At the time of diagnostic laparotomy, splenectomy, multiple liver biopsies, multiple lymph node biopsies and bone marrow biopsy using a 1 cm circular Stryker saw were obtained.

RESULTS

In 45 of 109 patients bone marrow involvement was identified, an overall incidence of 41%. The technique required to demonstrate the involvement is shown in Table II, comparing the results in the prospective series and the retrospective series previously reported (Jones *et al.*, 1972). The needle biopsy produced diagnostic material in 34 of the 43 patients in whom it was performed. The larger, open surgical biopsy demonstrated the disease in 13 patients, 2 of whom had a previous positive needle biopsy and 2 of whom had had no needle biopsy. In only 3 instances was a positive open biopsy obtained after a definitely negative needle biopsy.

TABLE II.—*Non-Hodgkin's Lymphomata Bone Marrow Involvement*

Needle biopsy	Open biopsy	Prospective series	Retrospective series
+	Not done	32	22
+	+	2	1
?	+	6	1
−	+	3	5
Not done	+	2	11
Total		45	40

Of the 328 patients at this institution who have had any form of bone marrow study at the onset of their disease, 81 have had marrow involvement—45 in this prospective study and 36 in the retrospective series reported by Jones (Jones *et al.*, 1972). The incidence of bone marrow involvement among the various histological subtypes is shown in Table III. The histiocytic lymphomata have a low incidence, whether nodular or diffuse. Those lymphomata with a mixture or predominance of lymphocytic cells have a higher incidence in both nodular and diffuse varieties. There is a very high incidence of bone marrow involve-

TABLE III.—*Non-Hodgkin's Lymphoma, Bone Marrow Involvement at Onset*

NLWD	0/3	—	DLWD	3/9	33%
NLPD*	40/73	55%	DLPD	9/31	29%
NM	13/68	19%	DM	10/38	26%
NH	1/25	4%	DH	5/75	7%
			DU	0/6	—

* 28/33 (85%) of prospective study patients.

ment in the nodular, lymphocytic poorly differentiated subgroup, with 28 of 33 (85%) prospectively studied patients having positive biopsies.

As in the previous report, the peripheral blood counts were poor indicators of bone marrow involvement. In only 3 instances was the peripheral absolute lymphocyte count greater than 4000/mm^3. Platelet counts and haemoglobin levels were usually within or near the normal range and not significantly different from the patients without demonstrable bone marrow involvement.

The serum alkaline phosphatase level was determined in all 45 patients and was a poor indicator of bone marrow involvement, as seen in Table IV. In only 4 instances was the level definitely elevated.

TABLE IV.—*Non-Hodgkin's Lymphomata, Bone Marrow Involvement*

Serum alkaline phosphatase levels	
Normal	38
Borderline elevations	3
Definite elevations*	4

* Greater than 150% of the upper limit of normal.

The clinical extent of disease in the 45 patients before bone marrow study and laparotomy was as follows: Stage I, one patient; Stage II 2 patients; Stage III, 35 patients; and Stage IV (other than bone marrow), 7 patients.

The association of liver and spleen involvement with bone marrow disease is seen in Table V. In 17 instances laparotomy was performed in patients who had bone marrow involvement, demonstrated either before or at the time of the laparotomy. Spleen involvement was not uniformly seen, though 13 of 17 (77%) instances were documented. Liver involvement was documented in 7 of 17 patients, (41%), given the sampling limitations of identifying lymphoma in the liver.

TABLE V.—*Non-Hodgkin's Lymphomata, Bone Marrow Involvement*

Associated involvement of liver and spleen	Liver	Spleen
Laparotomy confirmed, 17 patients	7 (41%)	13 (77%)
Laparotomy not done, 28 patients	2 (7%)	11 (39%)

DISCUSSION

This report confirms and extends the observations made by Jones *et al.* in a retrospective review. In this prospective study, in which 109 consecutive previously untreated patients were subjected to uniform diagnostic studies, 45 patients with bone marrow involvement were demonstrated.

The value of the biopsy technique must be re-emphasized, since a definitive diagnosis by the aspiration technique has been possible in only 11 of 92 patients in our combined series. Peripheral blood abnormalities are not helpful in selecting patients at high risk for bone marrow involvement. In contrast to Hodgkin's disease (Rosenberg, 1971), the serum alkaline phosphatase level is usually normal, as are skeletal x-rays and skeletal scans.

The major clinical correlations with bone marrow involvement are clinical extent of disease and histological subtypes. Bone marrow involvement occurs almost exclusively, at onset of the disease, in patients with at least clinical Stage III extent of disease. Of 45 patients with bone marrow involvement in this prospective study, and 36 patients with bone marrow in our retrospective review, only 5 had clinical Stage I or II disease.

The very high incidence of demonstrable bone marrow involvement in the nodular lymphocytic, poorly differentiated group is striking. To demonstrate such involvement in 85% of the patients of this subtype, given the sampling problems of a random needle biopsy, suggests that all of these patients have had generalized disease by the time they had been diagnosed. This is the most common subtype of the nodular lymphomata and accounts for almost one third of all patients with

non-Hodgkin's lymphomata, according to our current studies (Rosenberg, Dorfman and Kaplan, 1975). Yet these patients have a favourable natural history, with median survivals of 4–6 years, despite their relatively advanced age at onset. It should not be presumed that the demonstration of bone marrow involvement by relatively aggressive diagnostic techniques in patients who do not have apparent bone marrow dysfunction carries a poor prognosis. However, efforts to eradicate the disease must take into account the likelihood of bone marrow involvement.

In contrast, the frequency of demonstrable bone marrow infiltration in patients with the histiocytic subgroups, both nodular and diffuse, is low. Less than 10% of these patients have bone marrow disease, even when their clinical extent is widespread and other extranodal sites are evident. Yet, their prognoses are the poorest.

It remains to be determined if special handling of aspirated bone marrow material might be as informative as the biopsy techniques. Liao (Liao, 1971), Lukes (personal communication), and Forseyn (personal communication) have obtained improved yields by different techniques. However, until these methods are performed in parallel with the biopsy techniques and the results are compared, it is not possible to recommend them.

It is suggested that using a Westerman-Jensen, Jamshidi or some other satisfactory needle, a bone marrow biopsy be obtained on all patients with non-Hodgkin's lymphoma and that it be obtained before lymphography and certainly before diagnostic laparotomy and splenectomy. The major indication for performing the marrow study is to influence management decisions. If the therapeutic approach will be palliative for a particular patient or for a particular histological subgroup, whether or not bone marrow involvement is present, then the marrow study would be unnecessary. However, if aggressive diagnostic studies leading to radiation therapy in an eradicative attempt is contemplated, marrow study is essential at an early stage in the diagnostic sequence. If investigators are attempting completely to eradicate all sites of lymphoma by chemotherapy trials alone or with irradiation, bone marrow study by the biopsy technique must be done along with appropriate clinical and radiological studies to document the completeness of the response.

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