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RELATIONSHIP OF HISTOLOGY TO SITE IN THE NON-HODGKIN'S LYMPHOMATA: A STUDY BASED ON SURGICAL STAGING PROCEDURES

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THE VALIDITY of histological classifications and grading of malignant neoplasms is dependent upon their correlation with natural history, prognosis and response to therapy. The varied terminology applied to the so-called non-Hodgkin's lymphomata has been confusing and classifications have been many and controversial. In the United States collaborative investigations of large series of patients with non-Hodgkin's lymphomata at Stanford University Medical Center (Goffinet *et al.*, 1973; Jones *et al.*, 1973; Kim and Dorfman, 1974) utilizing the terminology and classification proposed by Rappaport (1966) (Table I) have indicated its usefulness when applied to clinical studies. Employing the criteria proposed by Rappaport (Dorfman, 1973), we have studied the relationship of histological subtype to site and distribution of lesions in untreated patients with non-Hodgkin's lymphomata, subjected to surgical staging procedures. Detailed morphological descriptions of these studies have been submitted elsewhere for publication (Kim and Dorfman, 1974).

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

Nodular	Diffuse
Lymphocytic, well differentiated	
Lymphocytic, poorly differentiated	
Mixed lymphocytic and histiocytic	
Histiocytic	
Undifferentiated	

MATERIALS AND METHODS

The pathological findings in 84 patients with non-Hodgkin's lymphomata subjected to surgical staging procedures at Stanford University Medical Center have been correlated with the pre-operative clinical evaluation in order to assess the anatomical distribution of lesions. Staging procedures included laparotomy with splenectomy, including splenic hilar lymph nodes, selected biopsies of para-aortic and mesenteric lymph nodes, wedge and needle biopsies of the liver and open iliac crest bone marrow biopsy. The results of this study have been compared with those from previously reported observations in patients with Hodgkin's disease (Dorfman, 1971; Kadin, Glatstein and Dorfman, 1971).

RESULTS

Consistency of the histological pattern in multiple sites was observed in 84% of patients with non-Hodgkin's lymphoma. The incidence of abdominal involvement (61%) in patients with non-Hodgkin's lymphoma was greater than that encountered in patients with Hodgkin's disease (46%) (Table II). Nodular lymphomata showed a particular tendency for widespread dissemination by virtue of their involvement of abdominal organs (spleen, liver or abdominal lymph nodes) in 72% of patients and the bone marrow

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TABLE II.—*Relationship of Histology to Site in Hodgkin's Disease and Non-Hodgkin's Lymphomata* (Stanford University Series*)

Site	Hodgkin's disease (Dorfman, 1971) % Cases	Non-Hodgkin's lymphomata (Kim and Dorfman, 1974) % Cases
Abdomen	46	61
Spleen	42	34
Access. spleen	27	33
Splenic hilar nodes	56	54
Para-aortic nodes	30	40
Mesenteric nodes	6	56
Liver	4	16
Gastrointestinal tract	0	6
Bone marrow	4	22
Mediastinum	58	17
Waldeyer's ring	< 1	4

* Based on preoperative clinical evaluation and surgical staging procedures. (Reproduced by permission of the Editor of *Cancer, N.Y.*)

in 28%. In contrast, diffuse lymphomata showed a low incidence (34%) of abdominal involvement. Diffuse histiocytic lymphomata affected the spleen and the abdominal lymph nodes in only 28% of patients and the bone marrow in 11%.

A high incidence of mesenteric lymph node involvement by the non-Hodgkin's lymphomata (56%) contrasted with that observed by us in Hodgkin's disease (6%). Splenic involvement in non-Hodgkin's lymphomata (34%) paralleled our experience in Hodgkin's disease (42%) and 50% of the affected spleens weighed less than 200 g.

Non-Hodgkin's lymphomata showed a greater tendency to affect the bone marrow (22%) than Hodgkin's disease (4%). Furthermore, marrow involvement was more common with nodular lymphomata (28%) than with diffuse lymphomata (15%). Evidence of liver disease was far more common in the non-Hodgkin's lymphomata (16%) compared with Hodgkin's disease (4%).

The incidence of mediastinal involvement by the non-Hodgkin's lymphomata (17%) was much lower than that observed in Hodgkin's disease (56%). In contrast to our experience with Hodgkin's disease, where we did not encounter involvement of the gastro-intestinal tract in patients subjected to staging laparotomy, 6% of patients with non-Hodgkin's lymphomata showed evidence of gastric disease and one patient had a lymphoma affecting the appendix. Non-Hodgkin's lymphomata involved Waldeyer's ring in 4% of cases, whereas in those patients subjected to surgical staging procedures we have encountered only one patient with Hodgkin's disease involving the lymphoid tissues of the nasopharynx.

Morphological findings

Spleen.—The pattern of involvement of the spleen varied considerably according to cytological type. Lymphocytic lymphomata, whether nodular or diffuse, involved the spleen in a uniform fashion, manifesting grossly discernible nodules of uniform size, which on microscopic examination proved to represent enlarged and involved malphighian corpuscles. By contrast, histiocytic lymphomata, both nodular and diffuse, formed irregular large tumour masses, involving malphighian corpuscles and extending widely into the adjacent red pulp.

Bone marrow.—Our criteria for the diagnosis of bone marrow involvement included the presence of an infiltrate of cells showing cytological atypia, in addition to the distribution of these cells in a paratrabecular location. These features enabled us to differentiate lymphocytic lymphomata from benign lymphoid nodules. Focal marrow involvement, with

the production of nodules of atypical cells, was a feature of lymphomata of both the nodular and diffuse type. The latter designations are thus applicable only to the architectural patterns observed in lymph nodes.

Liver.—Focal involvement of the liver by both lymphocytic and histiocytic lymphomata primarily involved the portal triads, with extension of the lymphomatous infiltrate into the adjacent hepatic parenchyma. The observation of cytological atypia was the most helpful criterion differentiating lymphomatous involvement from nonspecific lymphocytic infiltrates (so-called portal triaditis).

Lymph nodes.—With both nodular and diffuse lymphomata we occasionally encountered focal involvement of paraaortic and mesenteric lymph nodes with partial maintenance of the normal nodal architecture.

DISCUSSION

While some doubt has recently been cast on the scientific validity of the classification proposed by Rappaport, the results of this study add weight to previously reported observations that his classification can be successfully applied to clinicopathological investigations. Previously reported studies have emphasized the favourable prognosis of the nodular lymphomata (Dorfman, 1964; Jones *et al.*, 1973; Rappaport, 1966; Rappaport *et al.*, 1956) particularly of the lymphocytic and mixed cell type, when compared with diffuse lymphomata of corresponding cell types. Paradoxically, in patients subjected to surgical staging procedures, the nodular lymphomata showed a wider degree of dissemination of lesions, with a higher incidence of involvement of the spleen, abdominal lymph nodes, liver and bone marrow than the diffuse lymphomata. This implies that with the exception of Stage 1 disease, clinical staging of the non-Hodgkin's lymphomata is of less significance than is the histological type of lymphoma in the assessment of response to therapy and prognosis. Our previously reported studies have also emphasized the fact that nodular lymphomata should be regarded as distinct clinicopathological entities by virtue of their increased incidence in female patients, their extreme rarity in children and adolescents and the very low incidence in black patients (Dorfman, 1964, 1973; Jones *et al.*, 1973).

By virtue of the results of a number of investigations, which we and others have presented at this symposium, there are now valid reasons for questioning the validity and scientific accuracy of the term " histiocytic " when applied to cells of the nodular lymphomata and some of the diffuse lymphomata. It is quite likely that in many instances these large cells represent large transformed or atypical lymphoid cells. Nevertheless, the above described pathological and clinical observations emphasize the imperative need to separate lymphomata of the small lymphocytic and large cell " histiocytic " type by virtue of the distinct differences in the distribution of lesions and the variations in their natural history and in their response to therapy.

The anatomical distribution of lesions in the non-Hodgkin's lymphomata differs considerably from that observed in patients with Hodgkin's disease. Perhaps most significant is the high incidence of mesenteric lymph node involvement by the non-Hodgkin's lymphomata contrasted with the low incidence in Hodgkin's disease, an observation which has important implications in the planning of radiation therapy. Mesenteric lymph node involvement represents occult disease not demonstrable by lymphangiography. Splenic involvement in non-Hodgkin's lymphomata compares similarly with that experienced in Hodgkin's disease and approximately 50% of affected spleens are of normal weight and size and will not be detected by clinical methods.

Non-Hodgkin's lymphomata showed a greater tendency for dissemination to liver and bone marrow in untreated patients subjected to surgical staging

procedures when compared with Hodgkin's disease. The incidence of mediastinal involvement in non-Hodgkin's lymphomata was, however, much lower than that observed in Hodgkin's disease. Recent observations made on children with non-Hodgkin's lymphomata at the Stanford Children's Hospital have also shown that mediastinal lymphomata are associated with a high risk of the development of leukaemia (Glatstein *et al.*, 1974). These lymphomata are most often of the diffuse, poorly differentiated lymphocytic type.

The gastrointestinal tract and the lymphoid tissues of Waldeyer's ring were more commonly involved by the non-Hodgkin's lymphomata than by Hodgkin's disease. Although less frequent in association with non-Hodgkin's lymphomata than with Hodgkin's disease, we nevertheless have observed identical isolated sarcoid-like granulomata in the spleen, liver, lymph nodes and bone marrow. Their presence has not influenced our staging criteria and they are not considered to represent evidence of lymphomatous involvement of the respective organs in which they are identified. While their significance is at present obscure, it is likely that they represent a manifestation of an abnormal immunological reaction, in patients with both Hodgkin's and non-Hodgkin's lymphomata.

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