Relationship of Histology to Site in Hodgkin’s Disease

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Summary

The histological classification recommended at the Rye Conference, “Obstacles to the Control of Hodgkin’s Disease,” has been applied to a series of 185 untreated patients subjected to the surgical staging of Hodgkin’s disease at Stanford University Medical Center. The use of consensus findings of a panel of pathologists, in 114 of these cases, has confirmed the applicability and reproducibility of this classification. The pathological findings were correlated with the preoperative clinical evaluation in order to assess the anatomic distribution of lesions. Constancy of the histological pattern in multiple lesions was verified. The nodular sclerosing type was observed in 74% of cases and showed a predilection for the mediastinum (71%) with a high incidence of abdominal involvement (42%). However, the risk of abdominal involvement was greater with mixed cellularity (62%) and lymphocyte predominance (46%) types. Two of 3 patients with lymphocyte depletion had abdominal disease. In striking contrast to the nodular sclerosing type, no patient with lymphocyte predominance showed evidence of mediastinal disease. A high incidence of splenic involvement in patients was noted (42%) including 62% with mixed cellularity, 39% with nodular sclerosis, and 23% with lymphocyte predominance. With the exception of 2 cases of lymphocyte depletion involving the bone marrow and one case of mixed cellular type involving the lung, all other “extranodal” lesions were of the nodular sclerosing type. The anatomic distribution of lesions was unrelated to age or sex.

Introduction

In a recently completed study of 117 untreated patients subjected to laparotomy and open iliac crest bone marrow biopsy for the staging of Hodgkin’s disease at Stanford University Medical Center (18), the pathological findings were correlated with the preoperative clinical evaluation in order to assess the anatomic distribution of lesions. The validity and applicability of the modified classification of Lukes and Butler (22, 24) were confirmed, by virtue of its reproducibility when 2 pathologists independently reviewed all the lymph node biopsies. Separate evaluation by 2 of us resulted in concurrence in 94% of these cases. Furthermore, the consistency of the histological pattern in multiple lesions from the same patient was verified by comparing the findings in peripheral lymph nodes with those observed in lesions from the spleen and abdominal lymph nodes. This study also disclosed a striking frequency of occult disease in spleens of normal weight and in splenic hilar lymph nodes.

I have now expanded this investigation to include an additional 68 untreated patients subjected to surgical staging procedures. This report concentrates particularly on the relationship of histological subtype to the anatomic site of lesions.

During the period of this investigation, my impression of a significant incidence of inguinal lymph node involvement by nodular sclerosing Hodgkin’s disease prompted a separate analysis of this phenomenon which is incorporated in this report.

Materials and Methods

Of 185 patients studied, 117 underwent surgical staging at Stanford University Medical Center, prior to the initiation of therapy, from 1964 to 1969. These were the subject of a previous report by Kadin et al. (18).

By comparison with other reported studies in which the Rye classification is used (2–4, 8, 10, 14, 15, 20–22), an unusually high incidence of the nodular sclerosing type of Hodgkin’s disease was encountered: 85/117 (73%). In retrospect, the inclusion of 13 cases of the so-called cellular phase (18, 32) characterized by the presence of hyperlobated “lacunar cells” with minimal or absent sclerosis could not adequately account for this preponderance. In view of the implications of these observations, in relation to both the natural history of Hodgkin’s disease and its response to therapy, the diagnostic biopsies from 114 of these cases were subjected to further scrutiny by Dr. Robert Lukes (Department of Pathology, University of California School of Medicine), Dr. Costan Berard, Head, Hematology Section, Laboratory of Pathology, NIH, and by me. All 3 are members of the Lymphoma Task Force Pathology Panel under the chairmanship of Dr. Henry Rappaport (7). Unanimity of opinion regarding subclassification was achieved in 102 of 114 cases (89%). I interpreted 6 of the disputed 12 cases as nodular sclerosis, cellular phase, while Dr. Lukes and Dr. Berard preferred to classify these as mixed cellularity with “lacunar cells,” but no sclerosis. Three of these patients had characteristic nodular sclerosis in laparotomy specimens. The reviewers were also impressed by the constancy of the histological subtype when comparing the diagnostic biopsy with laparotomy specimens.

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2 Address reprint requests to the author at Surgical Pathology, C-218, Stanford University Hospital, Stanford, Calif. 94305.
Relationship of Histology to Site

Chart 1. Distribution of histologically proven lesions below the diaphragm in 86 of 185 patients subjected to surgical staging procedures. No. in parentheses, no. of patients.

Table 1
Anatomic distribution of lesions by histological type in 86 patients with Hodgkin's disease detected below the diaphragm by staging laparotomy and open iliac crest bone marrow biopsy

<table>
<thead>
<tr>
<th></th>
<th>Lymphocyte predominance (6)</th>
<th>Nodular sclerosis (58)</th>
<th>Mixed cellularity (20)</th>
<th>Lymphocyte depletion (2)</th>
<th>Total (86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen (185)a</td>
<td>3</td>
<td>53</td>
<td>20</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>Accessory spleen (15)</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Splenic hilar lymph nodes (55)</td>
<td>2</td>
<td>20</td>
<td>6</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>Paraaortic lymph nodes (180)</td>
<td>3</td>
<td>37</td>
<td>11</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>Mesenteric lymph nodes (35)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Liver (185)</td>
<td>1</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Bone marrow (185)</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

a No. in parentheses, total no. of specimens examined.
b No. of patients in each category.

An additional 68 cases, explored during 1970, have been analyzed. Details of the surgical procedure, which includes splenectomy, selective paraaortic lymph node biopsy, wedge and needle biopsies of the liver, and open iliac crest bone marrow biopsy, have been reported elsewhere (9). The handling and preparation of specimens was described in our previous publication (18).

Analysis of the distribution of lesions has been approached in 2 ways. Firstly, the site of involvement by histological type has been tabulated in 86 patients with histologically proven disease detected below the diaphragm by staging laparotomy (Chart 1, Table 1). Secondly, these findings were correlated with an assessment of anatomic distribution of lesions based on preoperative clinical evaluation (11, 12, 26, 28) (Chart 2). Reliance has been placed on roentgenographic examination of the thorax and mediastinum, including whole-lung tomography, for the detection of pulmonary and mediastinal involvement in cases where thoracotomy was not indicated. Interpretation of the lymphangiogram has generally been accurate below the level of the second lumbar vertebra, in detecting paraaortic lymph node involvement (18). On several occasions, this interpretation took precedence over a negative paraaortic lymph node biopsy, when postlaparotomy films disclosed that the most abnormal nodes had not been excised.

Determination of liver involvement has provided the greatest problem. Liver function tests have proved to be unreliable indicators of hepatic disease (18) and a negative biopsy does not exclude liver involvement. Assessment of peripheral adenopathy, other than the positive lymph node biopsy, was based on careful palpation by experienced physicians, including in most cases Dr. Henry Kaplan, Chairman, Department of Radiology and Radiotherapy, and Dr. Saul Rosenberg, Chief of the Oncology Service.

While, in the majority of cases, bone marrow and bony involvement were confirmed by biopsy, other bony lesions were demonstrated by 85 Sr bone scans.

My impression that inguinal lymph node involvement by nodular sclerosing Hodgkin's disease was not uncommon prompted a separate study of 18 patients in whom inguinal lymph nodes were excised for diagnostic purposes.

In accordance with our previous study, the modified histological classification of Hodgkin's disease, recommended by the Nomenclature Committee at the Rye Conference (24), was utilized, namely lymphocyte predominance, nodular sclerosis, mixed cellularity, and lymphocyte depletion. In 13 cases, recognition of a cellular phase within the spectrum of nodular sclerosing Hodgkin's disease was justified by the observation of characteristic sclerosis in other lesions from the same patient. The anatomic distribution of lesions has also been correlated with the patient's age and sex in order to...
Chart 2. Distribution of lesions by histological type of Hodgkin's disease in 185 patients. Assessment of anatomic distribution of lesions is based on clinical evaluation together with pathological findings in biopsy and laparotomy specimens. No. in parentheses, no. of patients.

<table>
<thead>
<tr>
<th>Lymphocyte Predominance</th>
<th>Nodular Sclerosis</th>
<th>Mixed Cellularity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(13)</td>
<td>(137)</td>
<td>(32)</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Histological type</th>
<th>No. of cases</th>
<th>Abdominal involvement</th>
<th>Splenic involvement</th>
<th>Mediastinal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte predominance</td>
<td>13 (7%)</td>
<td>6/13 (46%)</td>
<td>3/13 (23%)</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>137 (74%)</td>
<td>58/137 (42%)</td>
<td>53/137 (39%)</td>
<td>98/137 (71%)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>32 (17%)</td>
<td>20/32 (62%)</td>
<td>20/32 (62%)</td>
<td>11/32 (34%)</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td>3 (2%)</td>
<td>2/3 (66%)</td>
<td>2/3 (66%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>185 (100%)</td>
<td>86/185 (46%)</td>
<td>78/185 (42%)</td>
<td>110/185 (58%)</td>
</tr>
</tbody>
</table>

determined whether these are dependent or independent variables.

**Results**

It is gratifying to observe essentially similar trends in the additional 68 cases as compared with our earlier study of 117 cases (18).

**Initial Biopsy.** Nodular sclerosing Hodgkin's disease continues to be the most frequent type encountered at Stanford Medical Center and comprised 137 of the total of 185 cases (74%) (Table 2, Chart 2). The pattern of mixed cellularity was observed in 32 cases (17%) and lymphocyte predominance in 13 (7%). Only 3 cases with lymphocyte depletion were encountered (2%). Two of these had previously been classified as mixed cellular and nodular sclerosis, respectively, in our initial series of 117 patients. After review with Dr. Lukes and Dr. Berard, I concurred with their reclassification of these cases in the lymphocyte depletion category.

**Intraabdominal Lesions.** Chart 1 and Table 1 illustrate the anatomic distribution and histological classification of lesions detected below the diaphragm in 86 of 185 patients subjected to laparotomy and open iliac crest bone marrow biopsy. Although nodular sclerosis was the most frequent histological type, both the mixed cellularity and lymphocyte predominance types showed a disproportionately higher incidence of abdominal involvement: mixed cellularity, 20 of 32 cases (62%); lymphocyte predominance, 6 of 13 cases (46%); and nodular sclerosis, 58 of 137 cases (42%) (Table 2). Two of the 3 patients with lymphocyte depletion had abdominal disease, but their number is too small to assess the significance of this observation.

In our previous study of 117 patients, we encountered only 4 cases in which the histopathology of intraabdominal lesions differed from that of the original biopsy. However, in 3 of these, multiple organ involvement was noted, and all other lesions conformed histologically with the initial biopsy. Thirty-five of the additional 68 cases studied had intraabdominal lesions, none of which showed any significant change in the histological pattern, other than variations in the degree of sclerosis, within the nodular sclerosing type.

**Spleen.** The previously reported frequency of Hodgkin's disease in the spleen was maintained in the additional 68 cases investigated. Thirty-five of the latter had abdominal disease, 33 with splenic involvement. Thus, of 185 patients subjected to laparotomy, 78 (42%) were found to have splenic disease. In 31 patients, the weight of the involved spleen was less than 200 g. Twenty-six of the latter cases were of the nodular sclerosing type, while 5 of these spleens showed the pattern of...
Table 3

<table>
<thead>
<tr>
<th>Histological Type</th>
<th>Mediastinal Involvement</th>
<th>Abdominal Involvement</th>
<th>Abdominal and Mediastinal</th>
<th>Peripheral Lymphadenopathy Only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular sclerosis</td>
<td>58</td>
<td>18</td>
<td>40</td>
<td>21</td>
<td>137</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>4</td>
<td>13</td>
<td>7</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Lymphocyte predominance</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>38</td>
<td>48</td>
<td>37</td>
<td>185</td>
</tr>
</tbody>
</table>

Without abdominal disease.
Without mediastinal disease.

Mixed cellularity. By histological type, the incidence of splenic involvement in the entire series is as follows: lymphocyte predominance, 3 of 13 (23%); nodular sclerosis, 53 of 137 (39%); mixed cellularity, 20 of 32 (62%); and lymphocyte depletion, 2 of 3 (66%) (Table 2). The incidence of splenic disease by histological type, in 86 patients with histologically proven abdominal involvement is as follows: lymphocyte predominance, 3 of 6 (50%); nodular sclerosis, 53 of 58 (92%); mixed cellularity, 20 of 20 (100%); and lymphocyte depletion, 2 of 2 (100%).

Abdominal Lymph Nodes. Nodular sclerosis was the most prevalent histological type in both paraaortic and splenic hilar lymph nodes (Table 1, Charts 1 and 2). We have previously emphasized that the sole site of detected abdominal disease in 4 patients involved splenic hilar lymph nodes, which are not demonstrable by lymphangiography. A total of 30 instances of Hodgkin's disease in splenic hilar nodes was observed, 20 of the nodular sclerosing type.

Only 1 additional case of mesenteric lymph node involvement was encountered. Thus, 33 of 35 mesenteric node biopsies did not show evidence of Hodgkin's disease or reveal histological changes associated with the effects of lymphangiography (16).

Liver. Lesions in the liver were usually so small and focal as to defy accurate subclassification. Furthermore, despite an appropriate stromal reaction, including atypical histiocytes and/or mononuclear "Hodgkin's cells," diagnostic Reed-Sternberg cells could not be identified in multiple sections from several of these lesions. Such lesions have nonetheless been interpreted as "consistent with Hodgkin's disease," in patients who have diagnostic evidence of the disease elsewhere. In 2 of 15 diagnostic biopsies, the characteristic features of nodular sclerosis were observed. For the purposes of this study, all liver lesions have been classified according to the histology in other involved organs. The mixed cellularity type showed the highest frequency of liver involvement [7 of 20 cases (28%)]; nodular sclerosis, 7 of 58 cases (12%); and lymphocyte predominance 1 of 6 cases (16%). The spleen was involved in all patients with hepatic disease.

Bone Marrow. Eight instances of bone marrow involvement were detected by open iliac crest bone marrow biopsy, despite previously negative Westerman Jensen needle biopsies. Six of these patients had nodular sclerosing Hodgkin's disease, and 2 showed the pattern of lymphocyte depletion in the initial lymph node biopsy. Histological subclassification of the marrow lesion was frequently difficult and, in several patients with typical nodular sclerosis elsewhere, the marrow showed diffuse fibrosis. Focal involvement, with normal intervening marrow, was also observed in other instances. Abnormal reticulin patterns were helpful in assessing such lesions.

Clinicopathological Correlation. Sites of involvement by histological type of initial biopsy, based on both clinical assessment and surgical staging, are illustrated in Chart 2. The incidence of mediastinal and abdominal involvement in relation to the histopathology of the original biopsy is shown in Table 3. Eight patients with mediastinal disease and 5 with abdominal disease had no peripheral adenopathy. All others with mediastinal and/or abdominal disease had cervical-supraclavicular lymphadenopathy.

Ninety-eight of 137 patients (71%) with nodular sclerosing Hodgkin's disease had evidence of mediastinal involvement, 58 (42%) without evidence of abdominal lesions. Fifty-eight patients (42%) with nodular sclerosis had intraabdominal disease, 18 (13%) without evidence of mediastinal involvement.

Twenty of 32 patients (62%) with mixed cellularity, 6 of 13 patients (46%) with lymphocyte predominance, and 2 of 3 patients (66%) with lymphocyte depletion had abdominal disease. In contrast to the nodular sclerosing type, no patient with lymphocyte predominance, 1 with lymphocyte depletion,
Consequently, all lymph node biopsies coded as nodular sclerosing Hodgkin's disease in the files of the division of cases, we did not specifically study inguinal lymph nodes comprised a total of 293 biopsies (including those excised at Surgical Pathology, Stanford University Hospital, during a 2-year period, 1969 through 1970, were analyzed. These 293 biopsies included 185 (74%) with evidence of mediastinal disease (Table 2).

Of those patients in whom clinical evaluation did not suggest evidence of disease below the diaphragm, occult lesions were observed in the spleen in 19 and splenic hilar lymph nodes in 8. The 3 predominant histological types were equally represented. The only 2 cases of lymphocyte depletion involving the abdomen were both associated with splenomegaly, massive in one instance, and with abnormal lymphangiograms.

We have previously described a distinct relationship between the incidence of left cervical adenopathy and abdominal Hodgkin’s disease in 48 patients and the rarity of subdiaphragmatic lesions in association with unilateral right cervical adenopathy (18). An analysis of 83 patients with both abdominal and cervical-supraclavicular disease further demonstrates the validity of this observation (Table 4). All but 4 had left cervical adenopathy. Conversely, 20 of 24 patients with unilateral right cervical lymph node disease had no evidence of subdiaphragmatic involvement. These relationships hold for each histological type.

Sites of involvement other than those described above are illustrated in Chart 2. With the exception of 2 cases of lymphocytic depletion involving bone marrow and 1 case of mixed cellular type involving the right lung, all “extranodal” lesions were of the nodular sclerosing type.

The sex distribution related to all histological types shows a preponderance of males to females of 1.48:1 (Table 5). However, the ratio of male to female patients with nodular sclerosis approaches equality. While nodular sclerosing Hodgkin’s disease involved 67% of males, 85% of females were so affected. Predilection for the mediastinum by this type of Hodgkin’s disease was equal in both male and female patients.

The 3 major histological types, lymphocyte predominance, nodular sclerosis, and mixed cellularity, showed a similar age distribution, with the peak incidence in the 3rd decade (Chart 3). However, the 3 cases of lymphocyte depletion involved patients in the 5th, 6th, and 7th decades, respectively.

**Inguinal Lymph Node Involvement.** While emphasizing the unexpectedly high incidence of nodular sclerosing Hodgkin’s disease below the diaphragm, in our previous report on 117 cases, we did not specifically study inguinal lymph node involvement. There appears to be a general impression that this is a very rare phenomenon in the nodular sclerosing type. Consequently, all lymph node biopsies coded as nodular sclerosing Hodgkin’s disease in the files of the division of Surgical Pathology, Stanford University Hospital, during a 2-year period, 1969 through 1970, were analyzed. These comprised a total of 293 biopsies (including those excised at laparotomy). Of these, 18 were derived from inguinal lymph nodes, 11 from the left and 7 from the right side. Ten patients were male and 8 female. Ten of the 18 patients were in the 3rd and 4th decades, 6 in the latter. However, the age curve was bimodal with a 2nd peak in the 7th (3 patients) and 8th decades (2 patients).

**Discussion**

Procedures for the routine surgical staging of Hodgkin’s disease at Stanford University Medical Center since July 1968 have provided a unique opportunity for studies of the anatomic distribution of lesions in a large series of untreated patients (9, 11, 12, 18, 19). However, accurate assessment of the relationship of histological type to distribution of lesions is somewhat clouded by the preponderance of the nodular sclerosing type encountered in this series and the limited numbers of the mixed cellularity, lymphocyte predominance, and lymphocyte depletion types, respectively. These findings are at variance with series of cases studied elsewhere in the United States (Refs. 3, 4, 22, and 34; C. W. Berard, personal communication) Great Britain (2, 13), Australia (15), Finland (10), Sweden (21), France (33), Germany (14), Italy (8), and Africa (Ref. 2; C. W. Berard, personal communication). Furthermore, statistically significant differences in the distribution of types of Hodgkin’s disease from one country to another were reported in the afore-mentioned series.
applied to studies of Hodgkin's disease in children (2, 3, 31, 33) as well as in adults.

Strum and Rappaport (31) have described a striking preponderance of nodular sclerosing Hodgkin's disease in the 1st decade of life, based on a study of the lymph node biopsies from 35 children. Ten of these were seen at the University of Chicago Hospitals. The remaining 25 were selected from consultation files and were presumably derived from widely disparate regions. Consequently, there is little basis for comparison with the patient population at Stanford Hospital.

In retrospect our inclusion of only 13 cases of the so-called cellular phase of nodular sclerosing Hodgkin's disease in a total of 137 cases could not adequately account for this discrepancy. The possibility of observer error in the classification of Hodgkin's disease has been discounted by the consensus findings of 3 pathologists, Dr. Robert Lukes, Dr. Costan Berard, and myself. Unanimity of classification was achieved in 89% of the lymph node biopsies from 114 of these cases. The value of the use of consensus findings of a panel of pathologists was well demonstrated in a similar study of the classification and histology of Hodgkin's disease carried out at the University of Chicago, under the direction of Dr. Henry Rappaport. The results of this study have been reported by Coppleson et al. (5). Gough has made similar observations (13). In his report on a series of cases studied in England, he has suggested the possibility of some preselection of cases as an explanation for the varying incidence of histological types in patients referred to different institutions throughout the world. However, as Gough emphasized, the suggestion that patients with apparently restricted anatomical distribution of Hodgkin's disease are being referred to institutions specializing in the radiation therapy of this disease does not adequately explain the 45% incidence of nodular sclerosis in the Manchester series compared with 74% incidence at Stanford. Studies of the epidemiology of the various subtypes of Hodgkin's disease are urgently needed in view of the important prognostic and therapeutic implications.

We have previously emphasized the constancy of histological features in multiple lesions from the same patient. Of 86 patients with disease below the diaphragm, only 4 had lesions differing histologically from the original biopsy. However, in 3 of these patients, other lesions conformed to the histological pattern of the initial lymph node biopsy. Strum and Rappaport (32) have reported similar observations in sequential biopsy material. These findings differ substantially from those reported by Smithers (29). In a study of Hodgkin's disease at the Royal Marsden Hospital, he stated that progression from one histological type to another is commonly seen—and nodes showing more than one type can be found at the same time in the same patient.

By virtue of the preponderance of cases with nodular sclerosing Hodgkin's disease, the latter was the most frequent histological type encountered below the diaphragm. However, the risk of abdominal involvement was highest in the mixed cellularity type (62%) and lymphocyte predominance type (46%) as compared with nodular sclerosis (42%). The number of patients with lymphocyte depletion is too small to be statistically significant.

Surgical staging has now very adequately demonstrated the inaccuracy of clinical assessment of disease below the diaphragm, in untreated patients. This applies particularly to the spleen. Banfi et al. (1), using a variety of clinical methods for the evaluation of abdominal lesions in 500 cases of Hodgkin's disease, reported only 2% incidence of splenic involvement. In a study of 246 patients with Hodgkin's disease, utilizing the modified Lukes and Butler classification, Landberg and Larsson (21) reported abdominal involvement in only 2% of 49 patients with lymphocytic predominance and nodular sclerosis, compared with 27% of 100 patients with mixed cellularity and lymphocyte depletion. None of their patients was subjected to lymphangiography. They did not comment specifically on the incidence of splenic involvement.

Forty-two % of patients in this series had splenic involvement. The incidence was highest in the lymphocyte depletion type (66%) and mixed cellularity type (62%) and lowest in the lymphocyte predominance type. (23%). Perhaps the most striking observation was the presence of nodular sclerosing Hodgkin's disease involving the spleen in 39% of patients. Hanson (15), who did not have the benefit of surgical staging, was unable to detect evidence of nodular sclerosing Hodgkin's disease below the thorax, at the onset of the disease. Kaplan (19) has reported that the frequency of abdominal and particularly of splenic disease was underestimated in previous studies at this institution which did not include laparotomy and splenectomy.

In 86 patients with histologically proven abdominal lesions, 100% of the mixed cellularity and lymphocyte depletion types involved the spleen as compared with 92% of the nodular sclerosing type and 50% with lymphocyte predominance. Occult lesions, in patients unsuspected of any evidence of disease below the diaphragm, were observed predominantly in the spleen (19 patients) and splenic hilar lymph nodes (8 patients). In patients who were considered to have abdominal lymph node involvement by virtue of abnormal lymphangiograms, lesions were detected in 31 spleens weighing less than 200 g (26 with nodular sclerosing Hodgkin's disease, 5 with mixed cellularity). Conversely, a significant number of enlarged and palpable spleens did not contain histological evidence of Hodgkin's disease. This further emphasizes our previously reported observation (18) that the clinical assessment of splenic involvement by Hodgkin's disease is inaccurate in spleens weighing less than 400 g.

In our previous study, we recorded the detection of microscopic and focal lesions in abdominal lymph nodes with partial preservation of the nodal architecture. The focal nature and small size of such lesions in lymph nodes, as well as in the spleen and liver, undoubtedly account for the failure to recognize their presence preoperatively. Strum and Rappaport (30) have reported similar observations and have emphasized the significance of this finding in relation to diagnosis and staging. The surgical staging procedure at Stanford Hospital now includes left scalene lymph node biopsy since we have encountered several instances of focal, unsuspected lesions of both the nodular sclerosing and mixed cellular types in such biopsies.

We have also recorded the observation of isolated granulomas in this series of 185 patients (17, 18). Twenty-three (12.4%) had focal, noncaseating granulomas in tissues with no demonstrable evidence of Hodgkin's disease.
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No relationship to histological type was observed.

The incidence of liver involvement, detected by wedge and needle biopsy, was highest in the mixed cellularity type of Hodgkin's disease (28%). Sixteen % of lymphocyte predominance and 12% of nodular sclerosis cases showed evidence of liver involvement. As Kaplan (19) has emphasized, hepatic disease was invariably associated with splenic involvement.

Of 8 patients with bone marrow involvement, 6 had nodular sclerosing Hodgkin's disease. Of interest in this regard are the observations made by Franssila et al. (10) who reported that metastases to bone were demonstrated roentgenologically in 10 of 91 cases (22%) of Hodgkin's disease, all from the nodular sclerosis group.

The remarkable predilection of nodular sclerosing Hodgkin's disease for the mediastinum has been emphasized by others (4, 8, 10, 13, 15, 20–22). In this series 71% of patients showed evidence of mediastinal involvement by this type of Hodgkin's disease, unrelated to age, sex, or degree of sclerosis (Chart 2, Table 2). Of these, 42% did not have evidence of abdominal lesions. On the other hand, while 58 of 137 patients (42%) with nodular sclerosing Hodgkin's disease had disease in the abdomen, 18 (13%) of these did not have evidence of mediastinal involvement. Kaplan (19) had reported this seemingly noncontiguous distribution (“mediastinal skip”) in 31 of 340 cases (9%) of all histological types previously studied at Stanford Medical Center.

In contrast to the nodular sclerosing type, evidence of mediastinal involvement was not detected in patients with the lymphocyte predominance type, although 46% of these patients had abdominal disease. In a previous study at Stanford Medical Center, Keller et al. (20) had similarly failed to observe evidence of mediastinal disease in patients with the lymphocyte predominance type. While 62% of cases with mixed cellularity had abdominal disease, only 34% showed evidence of mediastinal involvement. One patient with lymphocyte depletion had roentgenological evidence of mediastinal disease.

In our previous publication (18), we stated that the consistency of histopathological patterns in multiple lesions and the frequency of intraabdominal involvement by all 4 histological types mitigate against the concept that these subtypes represent regional expressions of Hodgkin's disease (15, 23). However, the relationship of histological type to anatomic distribution of lesions in this series (particularly with regard to mediastinal involvement) provides some support for the concepts of Davidson and Clarke (6). They have postulated 2 clinical types of Hodgkin's disease. Type I (“superficial”) disease is characterized by involvement of superficial lymph nodes in the groins, axillae, and neck, often with coexistent disease in paraaortic and pelvic lymph nodes. Most cases of lymphocyte predominance and two-thirds of mixed cellularity fall into this category. Type II (“central”) disease primarily involves the mediastinum and contiguous areas in the lower neck and abdomen. “Central” disease comprises most cases of nodular sclerosis and one-third of mixed cellularity. Patients with lymphocyte depletion were excluded from their study because of the small number.

Whether or not such observations are valid, I fully agree with MacMahon (25) that the automatic classification of patients showing these histological features into the corresponding clinical type is inadvisable in the present state of our knowledge. Classifications which include too many variables inhibit analyses designed to evaluate the correspondence of such variables.

As recorded by others (4, 8, 10, 13, 15, 20), the relative incidence of nodular sclerosing Hodgkin's disease in this series is higher in females than it is in males (Table 5). However, predilection for the mediastinum by this type of Hodgkin's disease and the distribution of lesions elsewhere is similar in both male and female patients.

The age distribution is similar in regard to the 3 most frequent histological types, lymphocyte predominance, nodular sclerosing, and mixed cellularity, with a peak incidence in the 3rd decade (Chart 3). Although only 3 cases of lymphocyte depletion were encountered, these involved patients in the 5th, 6th and 7th decades, respectively. This reflects the experience of Franssila et al. (10), Gough (13), and Keller et al. (20), who reported that this type of Hodgkin's disease is more common in the older age groups.

In contrast to the reported frequency of involvement of Waldeyer's ring by other lymphomas (1), only 1 instance of Hodgkin's disease involving this site was observed in this series of 185 patients. This was of the lymphocyte predominance type. The infrequent involvement of mesenteric lymph nodes (2 of 35 cases) has resulted in the discontinuation of mesenteric lymph node biopsy as part of the routine surgical staging procedure for Hodgkin's disease unless these nodes are seen to be grossly enlarged.

Previous observations with regard to contiguity of spread between the left neck and abdomen (11, 19, 27, 28) have been substantiated in this series. Of 83 patients with both abdominal and cervical-supraclavicular disease, all but 4 had left cervical adenopathy. Of 24 patients with unilateral right cervical lymph node disease, only 4 had evidence of subdiaphragmatic involvement. These relationships hold for each histological type.

There has been speculation regarding the various histological patterns in Hodgkin's disease as reflections of differences in the state of host responsiveness (22, 23). This concept may be valid in relation to prognosis and patient survival. However, the disclosure by laparotomy of the unexpected frequency of abdominal involvement in patients with Hodgkin's disease of the nodular sclerosing and lymphocyte predominance types and the preponderance of extranodal involvement by the nodular sclerosing type in this study indicates that recognition of these patterns in the biopsy does not imply limited disease. While both male and female patients with nodular sclerosing Hodgkin's disease can be expected to have a high incidence of mediastinal involvement and those with lymphocyte predominance may have little if any evidence of mediastinal lesions, recognition of the various histological patterns, at the onset, is not a reliable indicator of the extent of disease elsewhere. The frequency of abdominal and particularly of splenic involvement by all 4 histological types and the observation that nodular sclerosing Hodgkin's disease involves inguinal lymph nodes, even in the aged patient, is convincing evidence supporting this contention.

In the light of these observations, the previously documented relationship of histological subtype to prognosis and survival (4, 8, 13, 15, 20, 21, 23) assumes even greater significance.
Relationship of Histology to Site

Conclusions

Application of the Rye classification of Hodgkin’s disease to a study of 185 untreated patients subjected to surgical staging procedures has confirmed its validity and reproducibility. A remarkable constancy of the histological pattern was observed in multiple lesions from the same patient.

An unexpectedly high incidence of abdominal and particularly splenic involvement was encountered in association with all histological types. The risk of such involvement was nevertheless greatest with the lymphocyte depletion and mixed cellularity types.

The striking predilection of nodular sclerosing Hodgkin’s disease for the mediastinum contrasted with the lack of any evidence of mediastinal involvement by the lymphocyte predominance type. A significant relationship between disease in the left neck and abdomen and the lower risk of abdominal involvement associated with unilateral right sided nodal disease was exhibited by all histological types.

The anatomic distribution of lesions was unrelated to age or sex.

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References

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