Evidence for an Orderly Progression in the Spread of Hodgkin’s Disease

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Summary

The sites of involvement of 100 unselected, untreated patients with Hodgkin’s disease have been studied. The extent of disease was determined by detailed clinical laboratory and radiologic survey, including lymphangiography and biopsy of equivocally involved areas. The initial site of extension of disease after high dose irradiation has also been analyzed in the 26 patients who developed new areas of disease.

It is apparent that areas of involvement or extension of Hodgkin’s disease are not random. Disease is found in adjacent lymphoid areas in the majority of patients. New areas of involvement were in areas immediately adjacent to the initial treatment fields in 22 of 26 patients. The mediastinum was the area most commonly skipped in the patients who demonstrated discontinuous involvement.

These observations support the concept that Hodgkin’s disease arises in a single site and spreads in a predictable manner along adjacent lymphoid channels. The therapeutic implications of these observations are presented.

Introduction

Until the etiology of Hodgkin’s disease is understood, we must continue to seek modifications of our present available modalities of treatment which might offer greater therapeutic benefit. The increasing acceptance of extended field radical radiotherapy for the initial treatment of Hodgkin’s disease provokes us to examine the rationale upon which it is based (4, 6, 7, 10–12, 16, 17). The major assumptions upon which this approach depends are that Hodgkin’s disease arises in a single focus, that its spread is relatively predictable to adjacent lymphoid regions, and that it remains confined to lymphoid regions accessible to tumoricidal doses of irradiation for a reasonable period of time. This does not exclude the possibility that systemic factors are of etiologic importance but suggests that the disease arises in a single site as do most other neoplasms.

Absolute evidence demonstrating the unicentric origin of Hodgkin’s disease is not available. However, there are now an increasing number of documented instances of complete eradication of the disease, without recurrence over the life-span of the individual and at post mortem, as a result of adequate irradiation to localized disease, implying that the disease was limited to the area of treatment (3, 5, 10, 17).

Yet Hodgkin’s disease is usually not limited to a single site when it is first discovered. The argument that for practical purposes it is a systemic disease has been supported by the relatively few documented cures appearing in the literature. Recently, however, improved results, even cures, have been described or projected for patients treated to several areas of involvement (4, 6, 7, 10–12, 16, 17). These results suggest that Hodgkin’s disease remains confined to the lymphatic tissues for a variable, but often considerable, period of time before true generalization occurs.

During the past 5 years, the availability of lymphangiography has greatly added to our ability to detect retroperitoneal sites of lymphomatous involvement (2, 14, 15). This has drawn greater attention to the importance of using every available technique to uncover disease in other areas. As a result, the gap between the true extent of disease and the known extent has narrowed, perhaps significantly.

After detailed clinical study, we have analyzed the sites of Hodgkin’s disease involvement in 100 consecutive untreated patients. It is quite apparent that there is not a random involvement with disease, but rather a fairly predictable pattern of sites of evident tumor. The majority of patients, prior to treatment, demonstrated disease confined to adjacent lymph node areas. In addition, when patients received adequate doses of irradiation to known areas of disease, the next site of involvement, if extension occurred, was usually an area adjacent to those originally involved.

These observations, to be presented in this report, support the concept that Hodgkin’s disease is a disease of unicentric origin that follows a predictable pattern of progression. The therapeutic implications of this concept will also be presented.

Case Material

During the past 3 years, we have had the opportunity to see 103 consecutive untreated patients with Hodgkin’s disease and to completely evaluate 100 of them. Three patients were not studied completely: 1 because of senility and 2 because of such obviously advanced disease that detailed diagnostic study seemed unwarranted. The majority of the remaining 100 patients were considered for inclusion in a controlled clinical study of the treatment of Hodgkin’s disease by radical radiotherapeutic technics (13). Though approximately ¼ of the untreated patients were ultimately rejected for this study because of patient refusal, prior treatment commitment, or disease outside of the lymph node areas, they represent an unselected group of patients seen at Stanford Medical Center during this time period.
The histologic diagnosis was confirmed by review of the biopsy material in all cases; only those patients with unequivocal Hodgkin’s disease are included in this analysis.

Diagnostic Methods

All patients had a detailed clinical history and physical examination by at least 2 physicians with considerable experience in the evaluation of patients with malignant lymphoma. Attention was paid to all peripheral lymph node areas and all palpable nodes were described, whether considered normal, abnormal, or equivocal. Whenever possible, lymph nodes of equivocal significance were biopsied.

Radiologic examinations included a posteroanterior and lateral chest film (in the past 2 years mediastinal and whole lung tomograms have been obtained); skeletal survey; upper gastrointestinal, small bowel, and barium enema studies; inferior venacavography; and bilateral lymphangiography. An excretory urogram is obtained with the inferior venacavogram.

Laboratory studies have included a complete blood count, platelet count, alkaline phosphatase, serum laetic dehydrogenase (LDH), serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), bromsulphthalein excretion at 45 min (BSP), serum uric acid, calcium and protein electrophoretic pattern, and 24-hr urine uric acid. Fecal fat and urobilinogen excretions were obtained in the majority of patients.

Bone marrow aspiration and an H & E section of the marrow clot were obtained in all cases. The majority of patients have also had a needle or open bone marrow biopsy.

Liver biopsy, either needle or open, was obtained in all cases of hepatic enlargement without liver function abnormalities and in those patients with 1 abnormality of liver function if the liver size was considered normal or equivocal. If 2 abnormalities of liver function were noted, or 1 abnormality was combined with definite hepatomegaly, involvement of the liver was assumed, even if a liver biopsy was normal.

The presence of delayed hypersensitivity was determined in the majority of patients utilizing a battery of 7 common antigens and/or a modification of the dinitrochlorobenzene (DNCB) test (1).

Whenever possible, equivocal evidence of retroperitoneal or splenic involvement was confirmed at exploratory laparotomy.

Staging of Disease

After complete evaluation, patients are staged at Stanford according to the following classification (18):

Stage 0. No detectable disease due to prior excisional biopsy.
Stage I. Single abnormal lymph node.
Stage II. Two or more discrete abnormal nodes, limited to 1 side of the diaphragm.
Stage III. Disease on both sides of the diaphragm, but limited to the lymph nodes, spleen, or Waldeyer’s ring.
Stage IV. Involvement of bone, bone marrow, lung parenchyma, pleura, liver, skin, gastrointestinal tract, central nervous system, kidney or sites other than the lymph nodes, spleen, or Waldeyer’s ring.

Stage I according to the Peters’ classification (16, 17).

Without systemic symptoms (A) With systemic symptoms (B)

<table>
<thead>
<tr>
<th>Stage</th>
<th>0</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>4</td>
<td>0</td>
<td>53</td>
<td>33</td>
<td>10</td>
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</tbody>
</table>

* Includes 6 patients who would be classified as Stage I according to the Peters’ classification (16, 17).

All stages are subclassified as A or B to describe the absence or presence of systemic symptoms, respectively. Documented unexplained fever of at least 1 week’s duration, severe night sweats, generalized pruritus, and unexplained recent weight loss of at least 10% of the normal body weight are accepted as systemic symptoms.

Using these staging criteria, these 100 untreated patients were classified into the groups listed in Table 1.

It can be seen that disease limited to a single lymph node is rare. Ten of the 100 patients would have been classified as Stage I according to the Peters’ classification, which defines Stage I as disease limited to a single anatomic region (16, 17). None of these patients had systemic symptoms. The frequency of systemic symptoms can be seen to increase as the extent of disease increases.

Therapy and Follow-up

The treatment of these patients was quite variable and not pertinent to the present discussion, except as it pertains to the site of recognized extension of disease after high dose irradiation. The majority of the patients were treated as part of a protocol described in an earlier communication (13). Only those patients who received at least 3000 rads to all areas of known involvement have been analyzed for sites of extension.

Patients are followed at frequent intervals after completion of their treatment by at least 2 experienced observers. They are seen at 1-month intervals for the 1st 6 months, 2-month intervals for the next 6 months, 3-month intervals for the 2nd year, and at 6-month intervals thereafter. Posteroanterior and lateral chest films, an abdominal flat plate, complete blood counts, a platelet count, and an alkaline phosphatase are obtained on each visit. Repeat skin testing is done at intervals.

The 1st extension of disease has usually been confirmed by biopsy, even by laparotomy if necessary.

Extent of Disease

The sites of demonstrated disease in the 100 patients who completed the detailed diagnostic evaluation are shown in Charts 1–4.

The entire regional area is indicated as involved if any disease has been found in the area.

It can be seen that 80 of these 100 unselected, untreated pa-
to the lymph nodes, spleen, and Waldeyer's ring, there was involvement of only contiguous areas. Random involvement of discontinuous lymphoid areas, as exemplified by disease in the neck and groin without involvement of intervening lymph nodes, was not seen. There were no examples of disease limited to 1 or both axillae.

In the remaining 8 patients in this group of 90 with involvement of only lymphoid structures, disease was found on either side of an area apparently free of disease. In 7 instances, the area skipped was the mediastinum. In 2 instances, the spleen was considered involved without demonstrated para-aortic or hepatic disease. In 1 patient, an axillary area was considered involved without evident disease in the ipsilateral neck. These 8 patients, with 10 examples of skipped areas are listed in Table 2.

The mediastinum and upper paraaortic areas are still relatively blind areas, despite recent advances in our diagnostic methods. Two of these 8 patients had therapy directed to the area apparently skipped and have shown no extension of disease to this area. Another patient had suspicious mediastinal enlarge-
Hodgkin's Disease
Extent of Involvement in 100 Untreated Patients

Eight patients with discontinuous involvement

Chart 3. Discontinuous involvement in 8 patients.

Hodgkin's Disease
Extent of Involvement in 100 Untreated Patients

Ten patients with Stage IV disease

Chart 4. Patterns of involvement in 10 patients with Stage IV disease.

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without interruption by mediastinal lymph nodes. This avenue of direct extension of abdominal carcinoma is known to all physicians. It is possible that Hodgkin's disease can spread via the thoracic duct in either direction between the neck and abdomen, without involving intrathoracic structures or the highest paraaortic nodes.

When disease was found outside of the lymphoid structures (Stage IV), even the extralymphatic areas of involvement were not entirely random. The patients with Stage IV disease are shown in Chart 4, indicating their areas of lymphoid involvement and their extranodal sites. Pleural and pulmonary disease were seen in patients with obvious mediastinal and/or hilar enlargement. Bone marrow involvement was usually associated with widespread disease in the untreated patients.

Sites of Extension

Twenty-six of these patients have had extension of their Hodgkin's disease to new areas after receiving irradiation doses of 3000 rads or more. In some instances, the therapy was delivered to known areas and to adjacent, apparently uninvolved areas, as per the protocol described previously (13). Chart 5 shows the initial area of extension in these patients as well as their areas of prior known involvement and their areas of treatment.

Twenty-two of these 26 patients extended to an area contiguous to their initial treatment field. Two patients apparently skipped untreated mediastinal or paraaortic areas, and 2 patients demonstrated bone marrow involvement as their 1st site of extension after all lymphoid areas were treated.

Discussion

In the past, the natural history of the progression of Hodgkin's disease has been obscured by diagnostic methods inadequate to uncover the true extent of disease. As a result, physicians noticing widespread lymph node enlargement concluded that this disease was different from most other neoplasms and that, like the leukemias, it arose in many foci simultaneously. Late in the course of the disease, almost any tissue or organ can be involved with the disease, and data from autopsy studies reinforce the opinion that Hodgkin's disease can disseminate hematogenously or is multicentric in origin (8). This attitude combined with the inadequate therapeutic programs formerly used has perpetuated the opinion that Hodgkin's disease is a systemic, uniformly fatal disease.

This concept gradually came under challenge by such students of the disease as Jackson and Parker (9), Craver (3), Gilbert (7), and Peters (16). However, true cures of the disease were still uncommon.

The advances in our diagnostic ability and the results of detailed study of patients early in their course provide convincing evidence that Hodgkin's disease does not raise multifocally. Before the distribution of disease has been altered by treatment the lymph node involvement is clearly not a random affair. Moreover, the great majority of patients, 80% of this series, had disease limited to the lymph nodes when first seen.

Even after initial radiotherapeutic efforts have controlled the apparent disease, the next site of involvement is not random.
Instead, 85% of the patients in this study in whom high dose irradiation was followed by any subsequent manifestation of disease, demonstrated disease, unrecognized in the initial evaluation, in areas immediately adjacent to the treated fields. There is no doubt that this predictability is lost late in the course of the disease as if there were a time when hematogenous spread occurred.

These observations give credence to the opinions of Gilbert (7), Peters (16, 17), Kaplan (11), and others (4, 6, 10) that in the initial approach to patients with Hodgkin’s disease it is reasonable to treat not only the known areas of involvement, but the areas immediately adjacent to the known disease. These adjacent areas are those most likely to contain disease undetectable by our present diagnostic methods. The degree to which these radical radiotherapeutic approaches might cure even widespread Hodgkin’s disease will be determined by the adequacy of available diagnostic methods, which tell us that such sites as the bone marrow, liver, and lung do not contain disease.

Controlled clinical studies to test these concepts have been initiated.

**References**

8. Hoster, H. A., Dratman, M. B., Craver, L. F., and Rolnick,
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Orderly Progression in Spread

Fig. 1. *Left:* roentgenogram demonstrating mediastinal Hodgkin's disease. *Right:* same patient demonstrating the uninterrupted thoracic duct following lymphangiography.
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