SIGNIFICANCE OF FOCAL INVOLVEMENT OF LYMPH NODES FOR THE DIAGNOSIS AND STAGING OF HODGKIN'S DISEASE

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Six cases of Hodgkin's disease in which lymph node biopsy sections demonstrated only minute foci of Hodgkin's disease are presented. The lymph node sections showed an essentially preserved nodal architecture and a cellular composition that in most areas was not suggestive of Hodgkin's disease. It is our intention to emphasize the need for careful examination of lymph node sections in which clues suggesting early involvement of a lymph node by Hodgkin's disease can be found. This is of great importance in both diagnosis and staging of the disease. The focal obliteration of subcapsular sinuses, the finding of foci of inflammatory cells, the discovery of atypical, malignant-appearing histiocytes, and an increase in the deposition of collagen, occasionally in a band-like fashion, should alert the pathologist to search for conclusive evidence of focal involvement of a lymph node by Hodgkin's disease.

ORDERLY PROGRESSION OF HODGKIN'S DISEASE to contiguous lymph nodes and lymph node groups was postulated by Rosenberg and Kaplan[2] on the basis of clinical and pathologic observations. Moreover, the observation that in a given lymph node group, some lymph nodes do and others do not contain evidence of Hodgkin's disease[3] is in keeping with this concept. This type of progression presumably occurs by direct extension through lymphatic channels and one can expect, and actually find in a certain number of instances, incomplete involvement of a biopsied lymph node that is submitted for study. At times, such involvement can be considered "focal" when only a very small area of a given lymph node section shows the diagnostic features of Hodgkin's disease. When this is associated with pronounced reactive hyperplasia, such areas can be readily overlooked (Fig. 1). For this reason, we wish to report our findings in 6 such instances from a rather large series of biopsy sections studied.

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MATERIALS AND METHODS

Four hundred and ninety-nine lymph node biopsies from 390 different patients diagnosed as having Hodgkin's disease at the University of Chicago Hospitals and Clinics were independently reviewed by 3 observers. These cases were impartially selected from the files of the Tumor Registry, Radiation Therapy Department, and the Department of Surgical Pathology; they included cases dating back to 1931. Each section was independently diagnosed and classified according to the classification of Lukes and Butler.[1] Of the above, 4 cases were noted to be of exceptional interest in that Hodgkin's disease could be identified in but a relatively small portion of the lymph node sections. The patient's clinical records were reviewed for pertinent information regarding original histopathologic diagnosis, the results of subsequent lymph node biopsies, and details of the patient's clinical course. The fifth case is one of a series of 14 now under active treatment at the University of Chicago in which laparotomy was done for staging purposes. In 4 of these, involvement of the spleen and/or retroperitoneal lymph nodes was demonstrated. In one of the cases with splenic involvement, a splenic lymph node was re-

moved and no evidence of Hodgkin's disease was found in the initial slide. When semi-serial sections were examined from this lymph node, however, a minute focus of Hodgkin's disease was discovered. The sixth case is that of a patient with known Hodgkin's disease recently readmitted to the University of Chicago Hospitals with symptoms of severe diarrhea and weight loss. An exploratory laparotomy revealed enlarged mesenteric lymph nodes which initially were interpreted as chronic lymphadenitis. Reexamination of semi-serial sections, as in the previous case, disclosed focal involvement of the lymph node by Hodgkin's disease.

RESULTS OF THE FIRST 4 CASES

Original histopathologic diagnosis: In 3 of the 4 original cases, an unequivocal diagnosis of Hodgkin's disease could not be made by the original observers. In one instance, a diagnosis of "lymphoid hyperplasia" was made, and, in two others, diagnoses of "paragranuloma (early Hodgkin's disease?)" and "probably early lymphoblastoma" were proposed.

Classification of original and subsequent lymph node biopsies: All 4 original cases were independently submitted to 3 observers for histopathologic classification. Second biopsies showing complete nodal involvement were available in 2 of the 4 cases and reviewed in the same manner. It was the responsibility of each observer to confirm the diagnosis and then to classify the biopsy section. The results are tabulated in Table 1.

It can be noted from Table 1 that the histologic classification of a lymph node section focally involved with Hodgkin's disease is quite difficult and a lack of consistency in classification, and, in one instance, diagnosis is demonstrable.

CLINICAL COURSE

In the 4 original cases, the signs and symptoms present at the time of biopsy were compatible with disseminated, rather than localized, Hodgkin's disease. It is apparent then that, although lymph node biopsy sections may show only microscopic foci of Hodgkin's tissue, the true extent of the disease may be much greater. In our study, bone destruction was evident in one case; symptoms of fever, night sweats and marked weight loss were present in two others; and, in the remaining case, a previous lymph node biopsy was said to be suggestive of Hodgkin's disease. In all cases, therefore, the finding of a microscopic focus of Hodgkin's disease in lymph node sections did not necessarily imply localized or early disease. An attempt was made to stage these patients despite the lack of lymphangiography and other modern staging techniques. This was correlated with survival (Table 2).

REPORT OF THE FIFTH CASE

A 26-year-old Caucasian female presented with a left supraclavicular mass of 4 weeks' duration. She had no symptoms, and physical examination was otherwise unremarkable. A biopsy of the supraclavicular mass was performed, and a diagnosis of Hodgkin's disease of the nodular sclerosing type was made. Subsequent staging techniques, including lymphangiography, were interpreted as normal. As part of a prospective study, the patient had a laparotomy with splenectomy and removal of splenic hilar lymph nodes and para-aortic lymph nodes. In addition, an open wedge biopsy of the liver was done. Upon microscopic review, sections of the spleen showed one small well-circumscribed area of Hodgkin's disease. Sections of the

TABLE 1. Histopathologic Classification of Original and Subsequent Lymph Node Biopsies

	Classification of biopsy I			Classification of biopsy II		
	Observers			Observers		
Patient	I	II	III	I	II	III
W.H.	Not H.D.	Unclassifiable	Mixed	Mixed	Diffuse fibrosis	Mixed
J.P.	Nodular sclerosing	Unclassifiable	Mixed	Reticular	Reticular	Reticular
V.P.	Mixed	Unclassifiable	Mixed	No subsequent biopsies performed.		
E.M.	All observers unable to classify.			No subsequent biopsies performed.		

TABLE 2. Staging and Survival (from Time of Biopsy) in Patients with Focal Involvement by Hodgkin's Disease

Patient	Original diagnosis	Stage	Survival (mos.)
W. H.	Lymphoid hyperplasia	IIB	5
J. P.	Paragranuloma (early H.D.?)	IIA	12
V. P.	Hodgkin's disease	IIIB	3
E. M.	Probably early lymphoblastoma	IV	14

various lymph nodes removed at laparotomy were examined and initially interpreted as reactive hyperplasia. However, upon review of additional semi-serial sections, a minute focus of Hodgkin's disease was discovered in a splenic hilar lymph node.

REPORT OF THE SIXTH CASE

A 23-year-old Caucasian man presented with a 3-week history of left cervical lymphadenopathy and easy fatigability. Within 1-½ months, masses appeared in the right cervical area and both axillae. No other signs or symptoms were present. A biopsy of the right cervical lymph node was performed and a diagnosis of Hodgkin's disease made. Although symptoms of fever, anorexia, and weight loss occurred soon after biopsy, subsequent staging procedures, including lymphangiography, were reported as normal. The patient, therefore, was considered Stage IIB and treated with radiation to a Maltese cross-portal in a dosage of 4500 rads in 6 weeks. Five months later, the patient was rehospitalized with symptoms of weakness and diarrhea. On admission, he was afebrile; physical examination disclosed no lymphadenopathy or hepatosplenomegaly. An upper gastrointestinal series showed small nodular lesions scattered throughout the small bowel. Chest roentgenograms, liver and spleen scans,

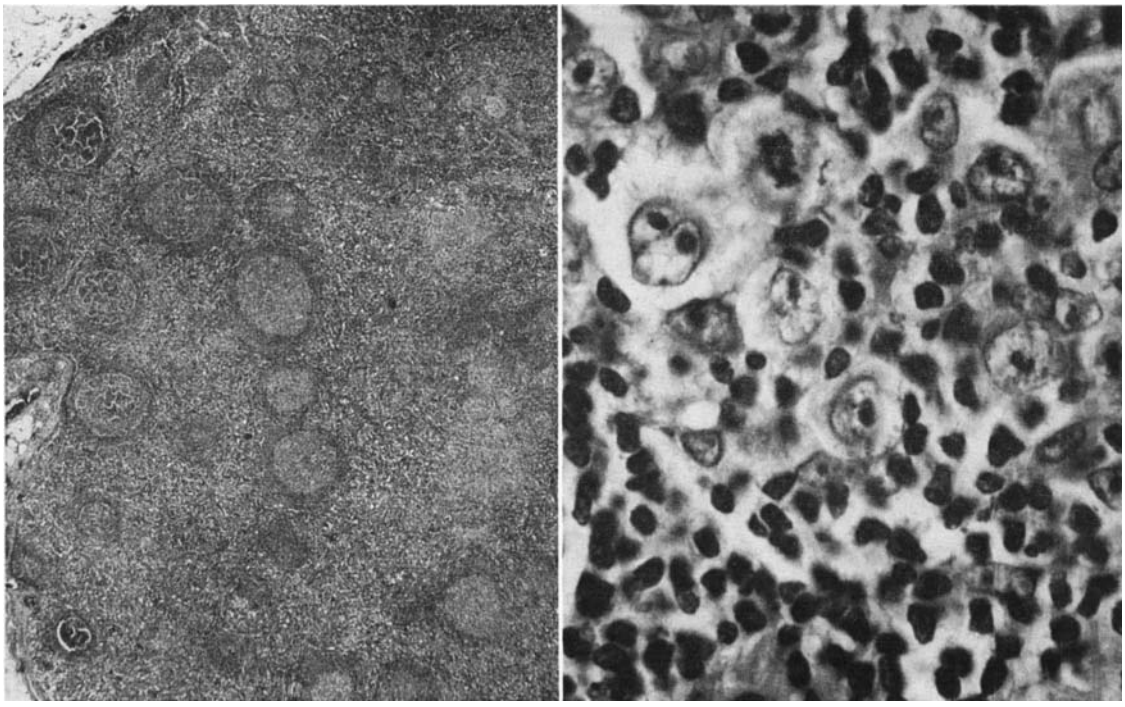

FIG. 1 *(left)*. Lymph node showing partial involvement by Hodgkin's disease. Note the reactive follicles and the partial preservation of the architecture in the left portion of the microphotograph as compared with the obliteration of the normal structure in the right portion. Thirty-nine-year-old Caucasian male with recurrent bouts of malaise and a history of weight loss. Lymph node enlargement was first noted in the right axilla followed by cervical node enlargement. This biopsy is from a right cervical lymph node. The diagnosis of Hodgkin's disease was followed by radiation treatment to the right neck and axilla. The patient died approximately one year after the diagnosis was established. The autopsy revealed generalized Hodgkin's disease (H and E, ×32).

FIG. 2 *(right)*. Same as Fig. 1 at higher magnification showing a focal area of histiocytes, one of which is binucleated and has the characteristic features of a Sternberg-Reed cell. A mitosis is also evident (H and E, ×1,240).

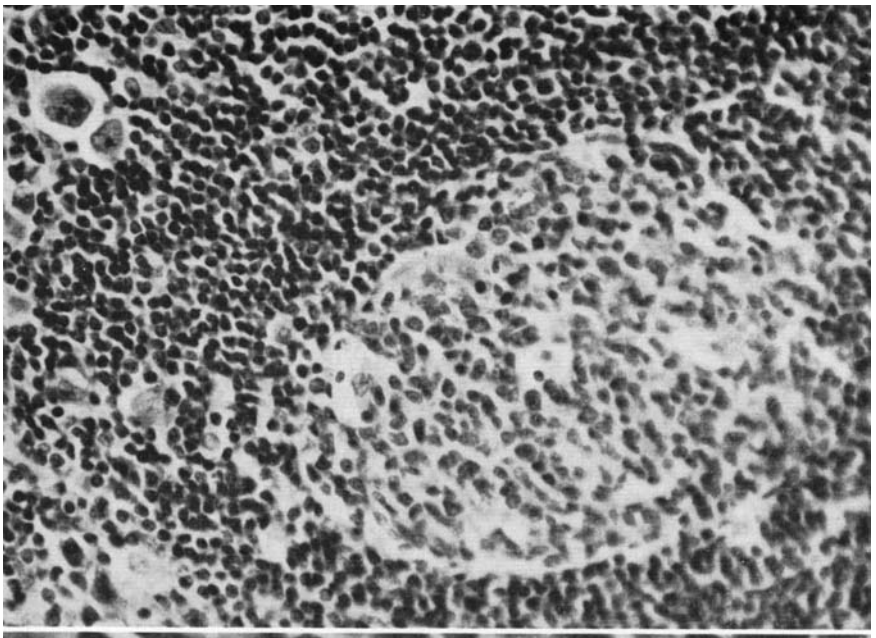

FIG. 3. A reactive follicle with a prominent germinal center is seen in the same field as a characteristic Sternberg-Reed cell. Thirty-nine-year-old Caucasian female who presented with a left cervical lymphadenopathy. The patient received radiation therapy to the cervical lymph nodes. She died 4½ years after clinical onset. No autopsy was performed (H and E, ×250).

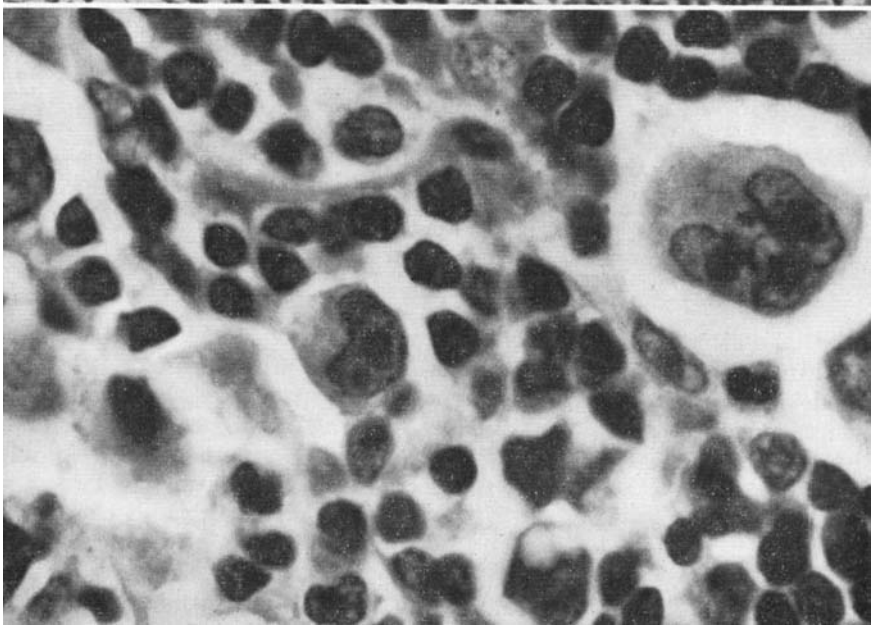

FIG. 4. High magnification of Sternberg-Reed cells illustrated in Fig. 3. A mononuclear malignant histiocyte with similar nuclear features is seen in the center of the illustration (H and E, ×1,400).

and a bone survey were all interpreted as normal. The patient underwent an exploratory laparotomy with removal of mesenteric lymph nodes and wedge biopsy of the right lobe of the liver. No masses were seen or palpated in the small bowel; the liver and spleen both appeared normal. Initial microscopic review of the mesenteric lymph node biopsy sections revealed "lymphoid hyperplasia with numerous prominent follicles and germinal centers. A marked sinus histiocytosis was noted as well as infiltration of the sinusoidal spaces by numerous plasma cells and eosinophils. The overall architecture of the lymph node was preserved." A diagnosis of chronic lymphadenitis was made. The liver showed lymphocytic infiltrates in the periportal areas with slight portal fibrosis and fatty change. Because of a previous positive diagnosis of Hodgkin's disease and because of the inflammatory elements in this biopsy, multiple deeper cuts from the tissue block of liver and lymph node were made. In the additional sections of the mesenteric lymph node, small

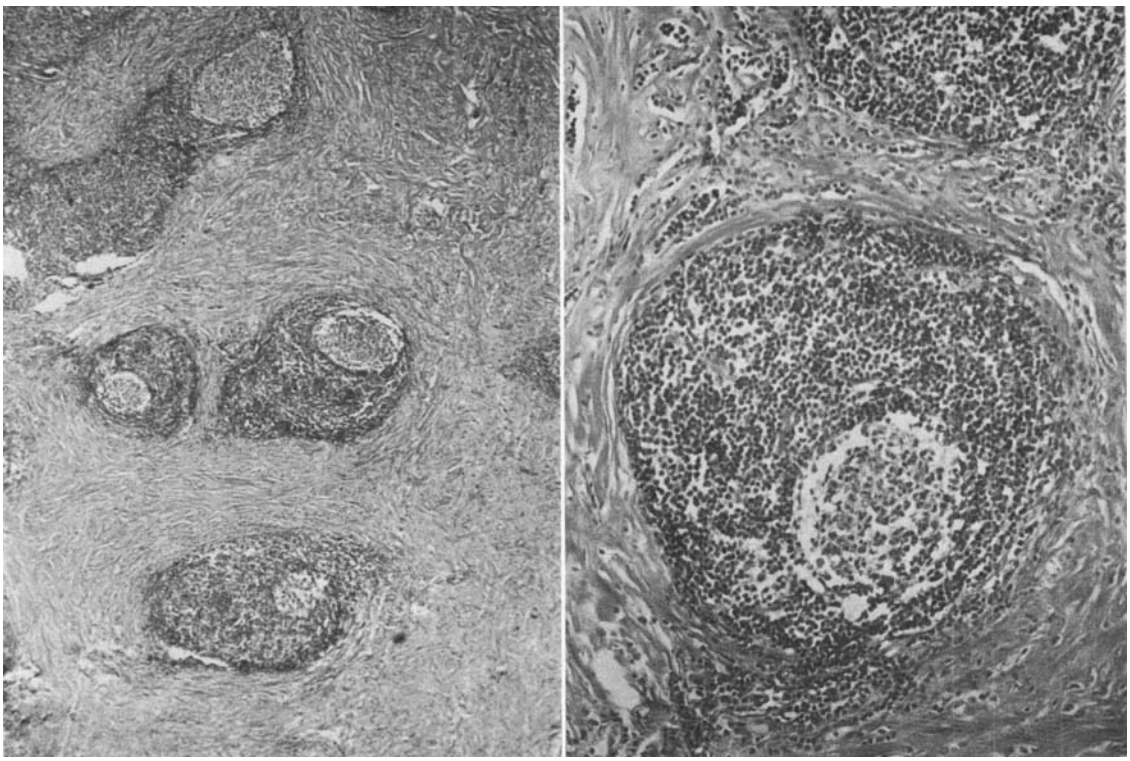

FIG. 5 *(left)*. Hodgkin's disease, nodular sclerosing type. This photomicrograph was taken from an area that is per se not diagnostic of Hodgkin's disease. Broad bands of collagen surround cellular, predominantly lymphocytic aggregates that contain reaction centers (H and E, ×35).
FIG. 6 *(right)*. Same as Fig. 5 at higher magnification (H and E, ×140).

areas of obliteration of the architecture were present and a few Sternberg-Reed cells identified, indicating focal involvement of the lymph node by Hodgkin's disease. In the liver, although atypical histiocytes were found, Sternberg-Reed cells were not seen.

DISCUSSION

It is reasonable to assume that lymph node involvement by Hodgkin's disease must, at one point in time, be focal, i.e., microscopic in nature. Clinically enlarged lymph nodes that appear merely reactive after brief and perhaps superficial examination with the light microscope may contain foci of Hodgkin's tissue. Although this may represent true focal or "incipient" Hodgkin's disease, it is more likely the result of sampling, particularly when the most accessible rather than the largest of a group of nodes is removed for histologic study.

The discovery of focal involvement is of great importance in the diagnosis and staging of Hodgkin's disease. When a focus of Hodgkin's disease escapes detection in a lymph node removed for diagnosis, treatment may be appreciably delayed. This is why we strongly recommend that in selecting a lymph node for biopsy the largest, rather than the most accessible, be chosen because the likelihood of extensive or complete involvement is much greater. However, if this advice is not heeded by the surgeon, the pathologist who examines the available lymph node carefully may still salvage the situation by being aware of the possibility of partial or focal involvement of lymph nodes and by taking proper precautions not to miss it. Even when the diagnosis is missed, the situation is not entirely irretrievable since frequently the symptoms and signs of Hodgkin's disease persist and repeat biopsies are requested and done. On the other hand, focal involvement of abdominal lymph nodes in instances which appear clinically to be Stage I and II disease is much more likely to occur than in symptomatic superficial lymph nodes removed for diagnosis. When

such involvement is missed, the situation is usually irretrievable because a second chance to do a laparotomy for staging purposes is practically nil. Failure to find Hodgkin's disease in abdominal staging procedures, therefore, may result in therapy that is not sufficiently extensive. For this reason, it is advisable to treat every abdominal lymph node in a patient with known Hodgkin's disease as a potential harbinger of microscopic involvement. This is illustrated by the fifth case in our study which revealed only one small, grossly appreciable focus of Hodgkin's disease in the spleen and a minute microscopic focus in a splenic lymph node. Had the spleen been negative for Hodgkin's disease, and had the lymph node not been semi-serially sectioned, the patient would have been considered Stage IA and received insufficient treatment. Again, in the sixth case, due to the discovery of focal involvement of a mesenteric lymph node, the patient was restaged and appropriate therapy begun. In view of the importance of detecting focal involvement, the following careful analysis of histopathologic features appears indicated.

1. Are all the subcapsular (marginal) sinuses intact or is there evidence of partial obliteration? A careful examination of the subcapsular sinuses may reveal areas of obliteration that contain foci of Hodgkin's disease.

2. Are there particular areas of the lymph node section where inflammatory cells are abundant? The finding of foci of eosinophils, neutrophils, and/or plasma cells may direct attention to areas of Hodgkin's disease.

3. Are the histiocytes normally present in the lymph node benign or reactive in appearance, or are there some with malignant features? The finding of histiocytes with large nucleoli and thick nuclear membranes should arouse suspicion and lead the pathologist to search diligently for characteristic Sternberg-Reed cells (Figs. 2–4).

4. Are there areas of the node section where bands of collagen appear? The finding of orderly bands of collagen, even to a limited degree, may represent early involvement by Hodgkin's disease of the nodular sclerosing type. In our study of Hodgkin's disease of the nodular sclerosing type, it was not uncommon to find areas in which numerous reaction centers were surrounded by orderly bands of collagen (Figs. 5, 6), but Sternberg-Reed cells were not demonstrable in these areas. In instances of this type it is imperative to search for characteristic Sternberg-Reed cells.

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