VASCULAR INVASION IN HODGKIN'S DISEASE: ITS INCIDENCE AND RELATIONSHIP TO THE SPREAD OF THE DISEASE

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Blood vessel invasion in Hodgkin's disease has rarely been reported in lymph node biopsies. Although this phenomenon may occasionally be noted in hematoxylin and eosin-stained sections, it is more readily demonstrable when elastica stains are employed. In all biopsy sections, the involved vessels were veins. Blood vessel invasion was most frequent in Hodgkin's disease with lymphocytic depletion, according to the Rye modification of the classification of Lukes and Butler; it occurred in approximately 50% of these cases. This high incidence in the reticular type of Hodgkin's disease was accordingly associated with the presence of extensive disease (80% of the patients with vascular invasion were stage III or IV) and with a relatively short survival. The phenomenon of blood vessel invasion in Hodgkin's disease tends to support the concept of Hodgkin's disease as a malignant neoplasm. It is essential to explain bone marrow and visceral involvements other than those occurring by contiguity.

INVASION OF LYMPHATICS, VEINS, AND ARTERIES by Hodgkin's disease has been noted by several authors.[3, 4, 8, 9, 15, 17–19, 22] Their observations, however, have usually been restricted to single case reports and brief statements to the effect that such involvement does occur. Of the 24 cases of Hodgkin's disease in which vascular invasion was reported, 23 were based on postmortem material. In one instance, vascular involvement was reported in both biopsy and autopsy sections.[9] The incidence of vascular invasion in lymph nodes removed for diagnostic study is not known. There are no studies in the literature correlating vascular invasion in biopsy material with other histopathologic aspects of Hodgkin's disease or with its clinical features. The present report deals with 18 cases in which blood vessel invasion was evident in lymph node biopsy specimens.

MATERIALS AND METHODS

The sections of 499 lymph node biopsy specimens from 390 individual cases of Hodgkin's disease were reviewed as part of a current clinicopathologic study. The occurrence of vascular invasion was incidentally noted during examination of tissue sections routinely stained with hematoxylin and eosin (Figs. 1–3); this observation was made prior to clinical review. Nine such instances were discovered in hematoxylin and eosin-stained sections and set aside for later reexamination and clinical correlation (Table 1). After their tabulation was completed, it occurred to us that this phenomenon might be more common than originally observed. A systematic search for vascular involvement was carried out, therefore, using paraffin sections stained for elastica by Weigert's method (Figs. 4–6). Biopsy specimens from 100 cases of Hodgkin's disease were selected at random.

The use of elastica stain was considered essential for such a survey since we believed that the cellular proliferation of Hodgkin's disease might have obscured or obliterated the vascular walls beyond recognition in hematoxylin and eosin-stained sections. Study

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TABLE 1. Vascular Invasion in Hodgkin's Disease Discovered Incidentally in Survey of 390 Biopsies without Special Stains

Patient	Age (yrs.)	Sex	Histologic type	Clinical stage	Survival following biopsy showing vascular invasion (mos.)
J. P.	14	Female	Nodular sclerosing	IIA	29
W. J.	52	Male	Mixed	IIB	1
E. M.	21	Male	Mixed	IIIB	48
J. Z.	62	Male	Mixed	IIIB	14
S. I.	30	Female	Mixed	Not available	65
A. K.*	53	Male	Lymphocytic depletion	IIIB	3
L. W.	60	Male	Lymphocytic depletion	IIB	14
W. A. J.	21	Male	Lymphocytic depletion	IIA	2
J. M.	58	Male	Lymphocytic depletion	IA	10

* This case is also listed in Table 3.

of sections stained for elastica resulted in the discovery of 10 instances of blood vessel invasion by Hodgkin's tissue. Of the original 9 cases with vascular invasion, one also happened to be included in our survey of randomly chosen cases. Thus, 18 individual cases of Hodgkin's disease in which biopsy sections revealed vascular invasion were assembled and reviewed. However, for comparative clinical and histopathologic correlations, only the 10 cases discovered on systematic survey of sections stained for elastic tissue will be used. All biopsy sections were classified according to the Rye modification of the classification

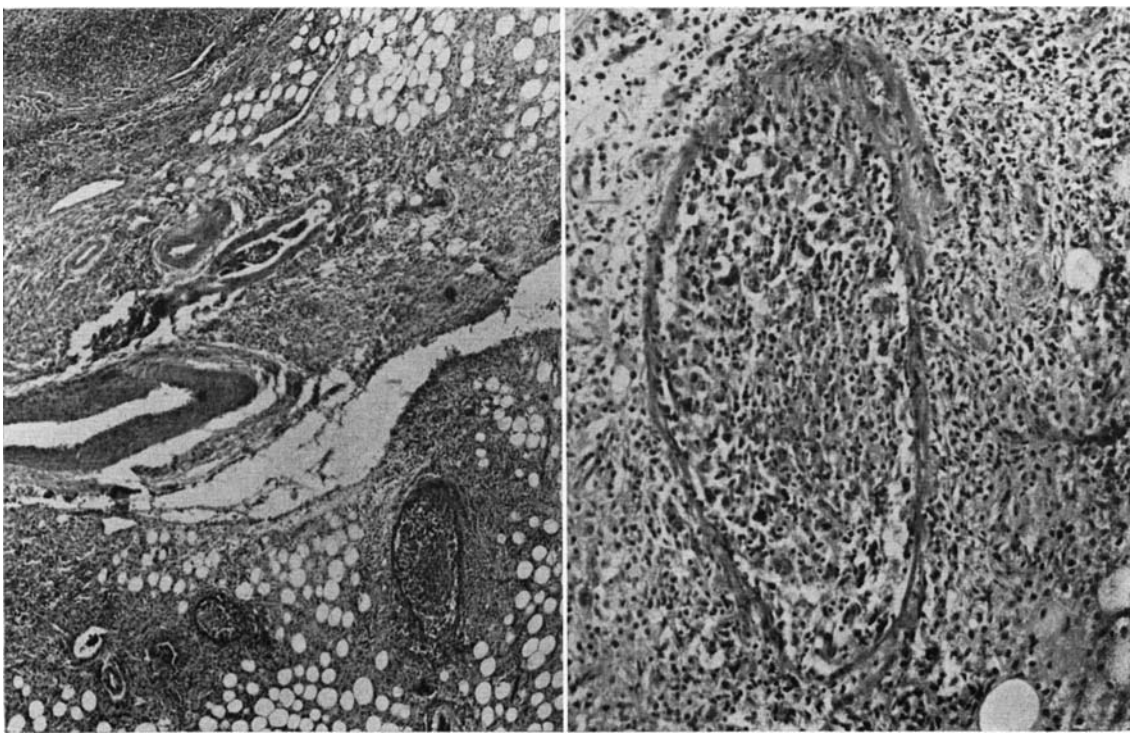

FIG. 1 *(left)*. Pericapsular fat tissue surrounding a lymph node showing Hodgkin's disease. The intravascular presence of Hodgkin's tissue is readily evident in routinely stained sections. Both involved vessels are veins (H and E, ×35).

FIG. 2 *(right)*. Same as Fig. 1 at higher magnification of the larger vessel illustrated in Fig. 1 (H and E, ×125).

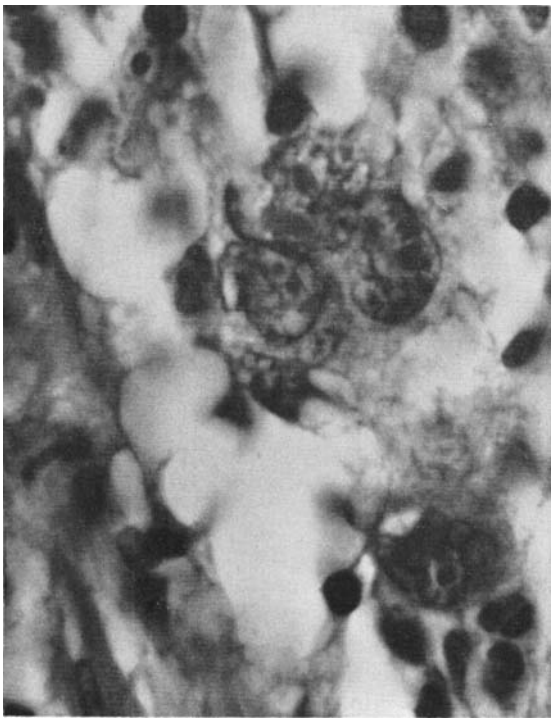

FIG. 3. Same as Fig. 1. Multinucleated neoplastic histiocytes with features of a Sternberg-Reed cell adjacent to intima of vessel wall (H and E, ×1,400).

of Lukes and Butler.[14] In addition to our own cases, the literature was reviewed for reports of vascular invasion in Hodgkin's disease.

REVIEW OF THE LITERATURE

Vascular invasion in Hodgkin's disease was first described by Dorothy Reed.[18] In a series of case reports she made special note of vascular invasion of lymphatics, veins, and arteries by the giant cells that bear her and Carl Sternberg's name. These giant cells, she stated, usually lie free in the interstices of the tissue, but are occasionally seen "on the reticulum" and have irregular protoplasmic processes. They occur in great numbers in the sinuses of the node, and occasionally appear in the blood vessels. "These cells have been frequently seen much elongated, passing between other cells, and in one specimen such a cell was apparently going through a vessel wall." Vascular involvement was again noted by Jeanselme and Marchal[9] in a case of "rapidly progressive Hodgkin's disease." They reported cellular nests composed predominantly of Sternberg-Reed cells within small blood vessels in a biopsy specimen (lymph node) and at autopsy (spleen, liver, pancreas, and lungs). These authors noted the frequent perivascular grouping of "Sternberg" cells, some of which appeared to be passing through vessel walls. Coronini,[4] in a study of autopsy material, carefully described the histologic features of the involvement of the walls and the invasion of the

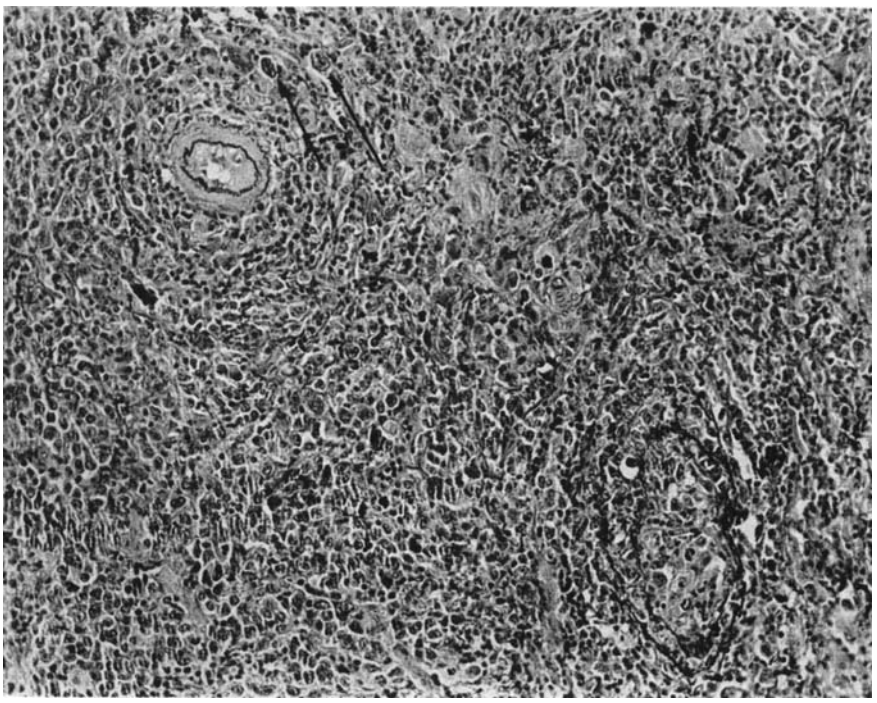

FIG. 4. Hodgkin's disease with lymphocytic depletion (reticular type of Lukes and Butler). Two Sternberg-Reed cells are evident (arrows). Note the preservation of the artery and the complete obliteration of the vein with partial destruction of the elastica in the wall of the latter. In the corresponding hematoxylin and eosin-stained section the presence of a vein could not have been suspected in this area (Weigert stain, ×160).

lumina of lymph vessels, veins, and arteries by the cellular proliferation of Hodgkin's disease. Callender[3] reported vascular invasion in a case of Hodgkin's sarcoma with an acute clinical course. Jackson and Parker,[8] in their discussion of the complications of retroperitoneal Hodgkin's sarcoma, observed "venous thrombosis due to compression by, and invasion from adjacent tumor."

Sayhoun and Eisenberg[19] described a histologic type of Hodgkin's disease which they termed "loosely cellular (rapidly progressing) Hodgkin's disease." This was quite similar to Hodgkin's sarcoma but differed in that it showed a mixed cellular composition with eosinophils, plasma cells, neutrophils, and lymphocytes, in addition to sheets of loose "reticuloendothelial" cells. They observed invasion of lymphatics and blood vessels associated with an "altered" blood picture. They mentioned, as did Reed, the marked vascularity of these tumors. Offerhaus[15] called attention to the occurrence of lymphatic and blood vessel invasion in cases of "reticulo-Hodgkin's disease." This histologic type, like that of Sayhoun and Eisenberg's, is intermediate between Hodgkin's granuloma and sarcoma; its clinical course, however, is more like that of Hodgkin's sarcoma. Rappaport, in his monograph on Tumors of the Hematopoietic System,[17] illustrated a tumor thrombus in an autopsy section of lung. This thrombus, found within a pulmonary vein, contained a characteristic Sternberg-Reed cell along with typical mononuclear and multinucleated histiocytes and many inflammatory cells. Varadi[22] described and illustrated a case of Hodgkin's sarcoma with vascular invasion of capillaries and arteries of both lymph node and lung tissue. Libánský et al.[12] observed

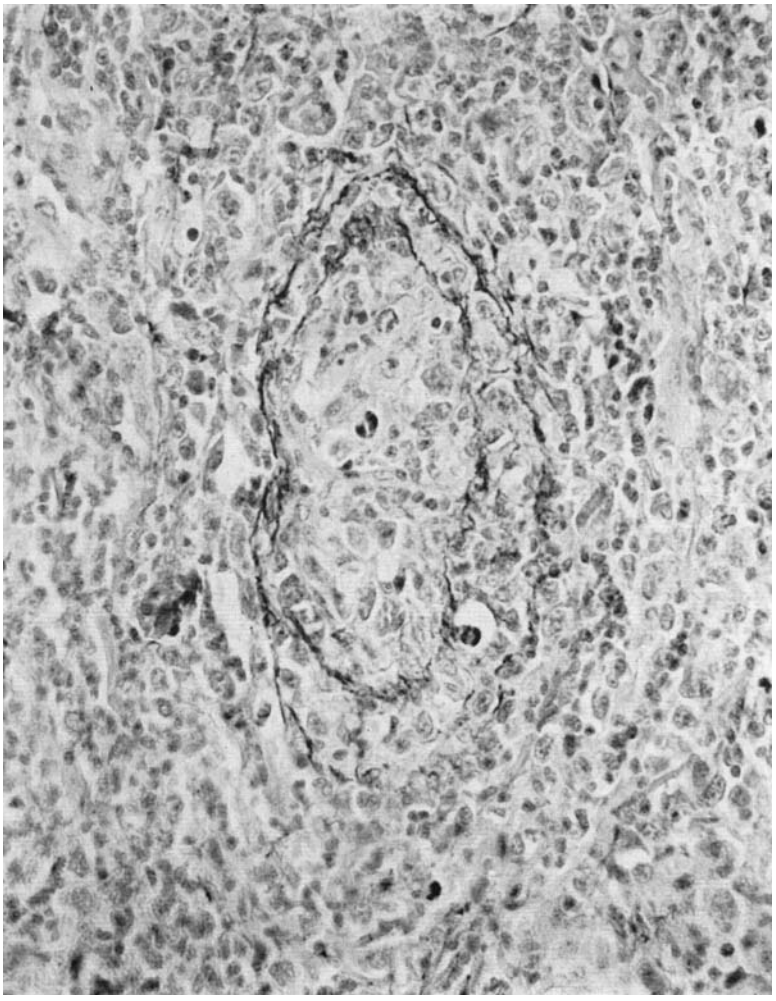

FIG. 5. Same as Fig. 4 showing the lumen of the vein completely filled by malignant-appearing histiocytes. This is sufficient for a diagnosis of vascular invasion by Hodgkin's disease as long as Sternberg-Reed cells can be demonstrated elsewhere in the sections (Weigert stain, ×310).

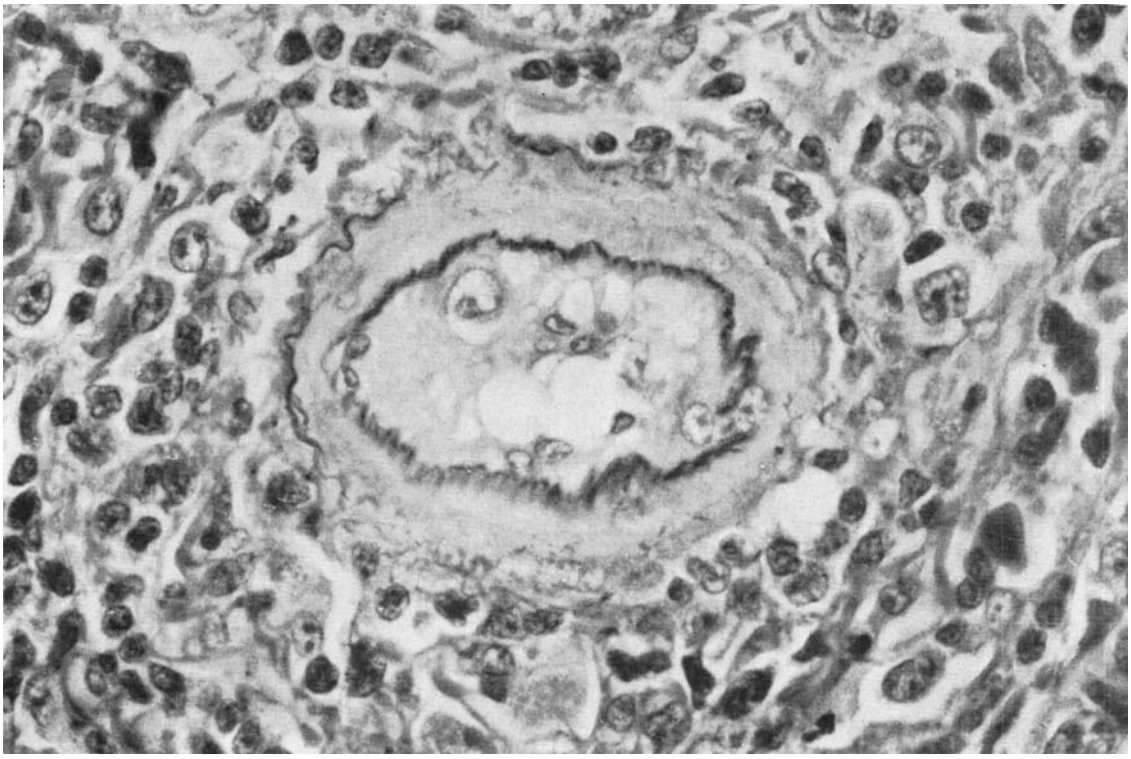

FIG. 6. Same as Fig. 4 illustrating the artery. No occlusive tumor thrombosis is evident, although one malignant-appearing histiocyte is seen within the lumen and another in the process of penetrating the arterial wall (Weigert stain, ×900).

and illustrated the relatively frequent localization of "lymphogranuloma" within the intima of blood vessels and the occasional intravascular occurrence of "Sternberg" cells. In their review of autopsy sections from 50 cases of Hodgkin's disease, 14 cases with involvement of the vasculature were noted; 90% of the invaded vessels were veins. The viscera most frequently involved were spleen (5 cases), liver (4 cases), lung (4 cases), and heart (1 case). In 4 cases, the paranodal vessels showed intimal invasion. The mean duration of the disease in their study was 2–½ years.

Haranghy et al.[6] described blood vessel changes in necropsy and autopsy sections. They observed "granulations" penetrating entire vessel walls and encroaching upon the lumen. In some cases, the destruction of elastic fibers as well as muscular elements was evident. These authors, however, failed to indicate whether or not neoplastic elements formed part of the invasive process; they merely stated that granulomatous vasculitis occurs in Hodgkin's disease. Finally, many investigators have described Sternberg-Reed cells in the peripheral blood of patients with Hodgkin's disease. They have not, however, correlated this observation with vascular invasion in lymph node biopsy sections.[1, 2, 7, 13, 16, 20, 21]

RESULTS

Frequency of blood vessel invasion: Reliable incidence figures can be based only upon the instances of vascular invasion which were discovered on systematic study of 100 biopsy specimens. In 10 of these, invasion of veins was demonstrated. Arterial invasion by Hodgkin's tissue was not evident, although in one instance individual atypical histiocytes were seen in the arterial lumen as well as in transit through the arterial wall. In about 10% of section of lymph node biopsies, therefore, vascular invasion, if carefully searched for, can be detected (Table 2).

Age and sex: There was no significant difference in the age distribution of cases with and without vascular invasion. The sex

distribution revealed more than twice as many females as males in the cases of vascular invasion discovered in our systematic survey. The significance of this finding, however, is questionable since our original series of 9 cases, discovered without elastica stains, showed an exactly opposite ratio. When all 18 cases were examined, therefore, the number of males equaled the number of females. Approximately the same ratio was found in our randomly chosen "control" group. The signs and symptoms most commonly present at the time of diagnosis in cases with vascular invasion were not significantly different from those seen in the control group.

Histologic types: Vascular invasion was clearly more common in Hodgkin's disease of the lymphocytic depletion type than in other histologic variants of the disease. Of 10 cases showing vascular invasion in our systematic study, 6 (i.e., 60%), were of this type. This represents a frequency of Hodgkin's disease of the lymphocytic depletion type that is more than four times as high as that found in our control group (i.e., 14%), and almost seven times as high as that in our general study of 255 pretreatment biopsy sections from patients with Hodgkin's disease (i.e., 9.5%). As seen in Table 3, 6 of 14, or approximately 50% of biopsy sections reviewed in our systematic survey and classified as Hodgkin's disease of the lymphocytic depletion type showed evidence of vascular invasion. In neither the original series nor in the survey of sections stained for elastic tissue was vascular invasion noted in Hodgkin's disease with lymphocytic predominance. Vascular invasion was seen, however, in both the nodular sclerosing and mixed cell types of Hodgkin's disease.

TABLE 2. Hodgkin's Disease

	Incidence of vascular invasion	
	No.	%
Hematoxylin and Eosin	9/390	2.3
Elastica-Weigert's	10/100	10.0

Staging: Because of the retrospective nature of this study and the infrequent use of modern staging procedures in the patient population under study, it was difficult to evaluate the accuracy of staging. Most cases in our study were staged according to the results of physical examination, chest roentgenogram, bone marrow aspiration, and liver function tests. In occasional cases, inferior vena cavography was employed; in no instance, however, had lymphangiography been used. Therefore, the staging of 3 patients as IIA in our group of 10 patients with vascular invasion may not reflect the true extent of their disease. With this in mind, 5 of 10 patients with vascular invasion were stage IV, 2 were stage III, and 3 were stage IIA. Four cases of Hodgkin's disease with lymphocytic depletion were stage IV, one was stage IIIB, and one was stage IIIA. One case of Hodgkin's disease of the nodular sclerosing type was stage IV. The remaining cases of the nodular sclerosing type and one case of mixed cell type represented the cases staged IIA (Table 4).

Survival: The total mean duration of the

TABLE 3. Lymph Node Biopsies Showing Vascular Invasion Listed by Histologic Types*

Histologic type	Biopsy section vascular invasion		All cases with vascular invasion	Distribution of type of 100 selected at random biopsies	Distribution by type of 255 consecutive pretreatment biopsies
	In original survey (H&E stain)†	Systematic survey (Weigert's elastica)‡			
Lymphocytic predominance	0	0	0	6 (60%)	32 (12.6%)
Nodular sclerosis	1 (12.5%)	3 (30%)	4 (22.2%)	38 (38%)	96 (37.8%)
Mixed	4 (50.0%)	1 (10%)	5 (27.8%)	39 (39%)	92 (36.0%)
Lymphocytic depletion	3 (37.5%)	6 (60%)	9 (50.0%)	14 (14%)	24 (9.5%)
Unclassifiable	0	0	0	3 (3%)	11 (4.1%)
TOTALS	8	10	18	100	255

* According to the Rye modification of the classification of Lukes et al.
† Cases from Table 1.
‡ Cases from Table 4.

TABLE 4. Vascular Invasion in Hodgkin's Disease Discovered with Elastica Stains in Survey of 100 Unselected Lymph Node Biopsies

Patient	Age (yrs.)	Sex	Histologic type	Clinical stage[11]	Survival following biopsy showing vascular invasion (mos.)
R. F.	9	Male	Nodular sclerosing	IIA	16
J. H.	65	Female	Nodular sclerosing	IIA	17
N. L.	20	Female	Nodular sclerosing	IV	50
M. L.	32	Female	Mixed	IIA	5
A. K.	53	Male	Lymphocytic depletion	IIIB	3
G. O.	33	Female	Lymphocytic depletion	IIIB	2
E. P.	65	Female	Lymphocytic depletion	IV	½
N. S.	37	Female	Lymphocytic depletion	IV	1
E. M.*	31	Male	Lymphocytic depletion	IV	6
L. B.†	33	Female	Lymphocytic depletion	IV	21

* Second biopsy: biopsy 1 performed 3 years earlier and classified as Hodgkin's disease—mixed.
† Second biopsy: biopsy 1 performed 2 years, 8 months earlier and classified as Hodgkin's disease—nodular sclerosing.

disease from the time of the biopsy showing vascular invasion was 13.0 months compared to 3.6 years in the total series (Table 4). Only one histologic type, namely Hodgkin's disease with lymphocytic depletion, was present in sufficient numbers to permit comparison of survival between the cases with and without vascular invasion. Of these, 6 cases with vascular invasion had a mean survival of 3.9 months; of 8 cases of Hodgkin's disease with lymphocytic depletion without vascular invasion, it was 8.3 months. The total number of cases in the other types was too small to permit any attempt at correlating histologic types and stages with survival. Moreover, as pointed out previously, because the material in this retrospective study preceded the time in which accurate staging procedures were used, the accuracy of the staging, as recorded in our series is questionable. A prospective study designed to include such correlations is in progress.

Laboratory findings: With respect to pretreatment hemoglobin, white blood counts, and absolute lymphocyte counts, no significant differences were noted between the cases with vascular invasion and the control group. Both groups exhibited a mild anemia in the range of 11–12 g/100 ml hemoglobin. The white blood counts ranged between 5–8,000 cells/mm^3; absolute lymphocyte counts prior to treatment ranged from 1500–2000/mm^3. At the time of diagnosis, however, lymphocytosis was noted in 30% of the cases with vascular invasion and in 42% of the control cases.

Microscopic observations: Only those cases were included in the series (Table 3) in which unequivocal intraluminal Hodgkin's tissue could be demonstrated. In 4 instances, characteristic Sternberg-Reed cells actually were evident within the intravascular tissue, and, in the remaining cases, malignant-appearing mononuclear histiocytes (reticulum cells) were present. Partial destruction of the vessel wall (Figs. 7–9) was demonstrable in 5 out of 10 cases.

In determining the presence of blood vessel invasion, certain pitfalls had to be avoided. For the diagnosis of this feature, we required that at least malignant-appearing histiocytes, if not characteristic Sternberg-Reed cells, be part of the invading tissue and that the proliferating tissue penetrate the vascular endothelium. The following histologic appearances were not regarded as conclusive evidence of vascular invasion.

1. Infiltration of the media and intima without penetration of the endothelial lining and without intraluminal appearance of the cellular proliferation; in most, if not all of these instances, the majority of cells infiltrating the vascular walls were inflammatory cells and malignant cells could not be clearly demonstrated. These changes were interpreted as indicative of phlebitis representing vascular involvement by the inflammatory reaction that was prevalent throughout the lymph nodes.

2. In some instances, elastica stains revealed complete obliteration of the lumen. Corresponding hematoxylin and eosin-stained

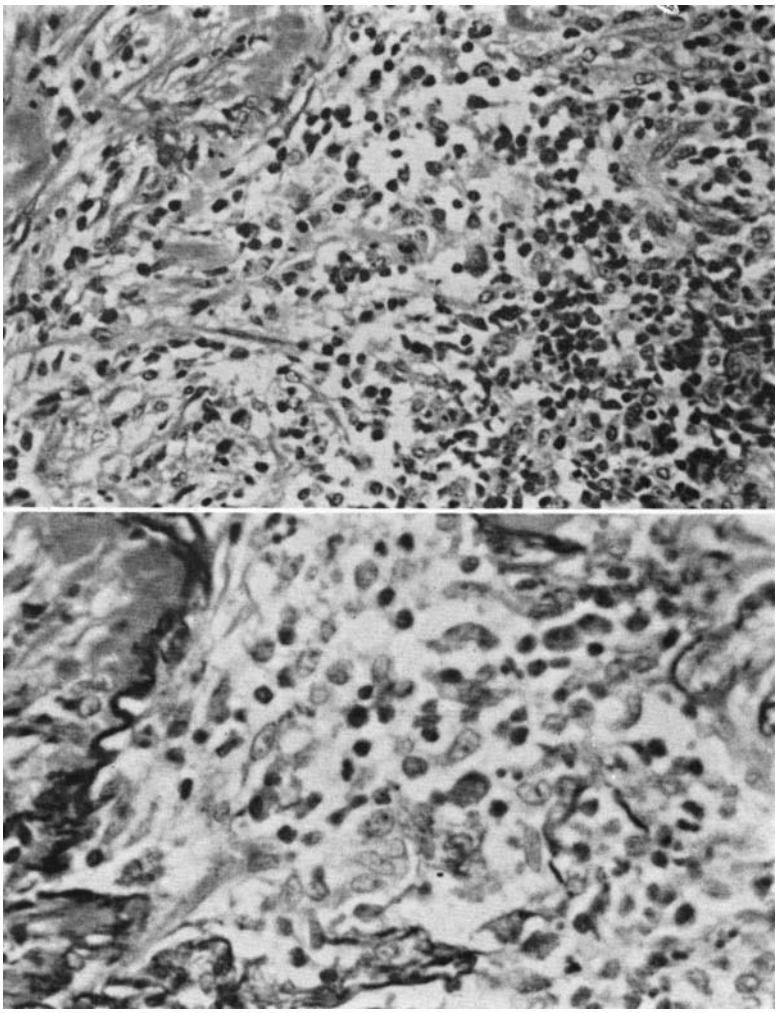

FIG. 7. Hodgkin's disease nodular sclerosing type. This area was recognized as a blood vessel only after a corresponding section (Fig. 8) was stained for elastic tissue. Note that on the left of the illustration it can be only vaguely surmised that this represents a vessel wall. In the approximate center of the field a typical Sternberg-Reed cell surrounded by a lacunal space is evident (H and E, ×400).

FIG. 8. Same as Fig. 7, elastica stain (Weigert stain, ×470).

sections showed an abundance of plasma cells to the almost complete exclusion of other cellular elements. These, too, were interpreted as chronic phlebitis.

3. Occasionally, both inflammatory and neoplastic cells were seen lying free within blood vessels that were otherwise not altered. These cells appeared to be floating in the blood plasma and were not present as cohesive tissue within the lumen of the vessels. A finding of this type was not regarded as absolute proof of vascular invasion by Hodgkin's disease since artifactual displacement of cells into vascular lumina could not be ruled out.

Vascular invasion in relation to other histologic features of malignancy: During an attempt to correlate the findings of blood vessel invasion with certain histopathologic features it became evident that this phenomenon was more likely to occur in the more malignant variants of Hodgkin's disease, although it was also observed in Hodgkin's disease of the nodular sclerosing type. The most striking feature was the observation that vascular invasion was prone to be associated with an abundance of malignant-appearing histiocytes. Using estimates of the proportion of malignant-appearing histiocytes in relation to total cell population, we found that in 4 instances malignant-appearing histiocytes constituted more than 50% of the cell population, in 6 instances more than 30%, in 8 instances more than 10%, and in only 2 instances, less than 10% of the cell population. Table 5 illustrates these figures in comparison with the prevalence of malignant-appearing histiocytes in the control group.

TABLE 5. Proportion of Malignant-Appearing Histiocytes ("Reticulum Cells") in a Random Sample of 100 Biopsy Specimens in Comparison with 10 of These That Showed Vascular Invasion

	Malignant-appearing histiocytes			
	<10%	10–30%	30–50%	>50%
100 cases selected at random (including the 10 cases below)	44	36	11	9
10 cases with vascular invasion	2	2	2	4

DISCUSSION

The observation of vascular invasion is of significance for 2 reasons: 1. It adds further weight to the contention that Hodgkin's disease represents a true neoplastic disorder, since vascular invasion and propagation of the disease by blood vessels represent one of the classical patterns of neoplastic dissemination; 2. It sheds further light on the mode of spread of the disease.

The presence of vascular invasion that involves not only the lymphatic vessels but also veins would tend to confirm the observation that orderly progression from one lymph node group to the other[10] is not the only pathway of progression of Hodgkin's disease, but that true hematogenous metastases may occur. Invasion of veins, the most common form of histologically observed vascular invasion may be one of the 2 pathways leading to visceral and bone marrow involvement, the other being via the thoracic duct.[5]

The absence of vascular invasion in Hodgkin's disease with lymphocytic predominance, and its relatively high incidence in Hodgkin's disease with lymphocytic depletion indicate that the general concept of varying degrees of aggressiveness and malignancy that is being employed for the assessment of neoplastic diseases in general also applies to Hodgkin's disease. It is particularly significant, however, that vascular invasion is not limited to that type of Hodgkin's disease in which neoplastic cells predominate but is also observed in instances in which inflammatory cells are abundant, such as Hodgkin's disease of the nodular sclerosing and mixed-cell types. Thus, inflammatory cells are associated with the neoplastic elements even when they invade blood vessels. This tends to indicate that the basic pattern of the histologic changes as expressed by the proliferation of neoplastic histiocytes and a host reaction of inflammatory cells is maintained even after the vessel walls are penetrated and tumor thrombi are formed.

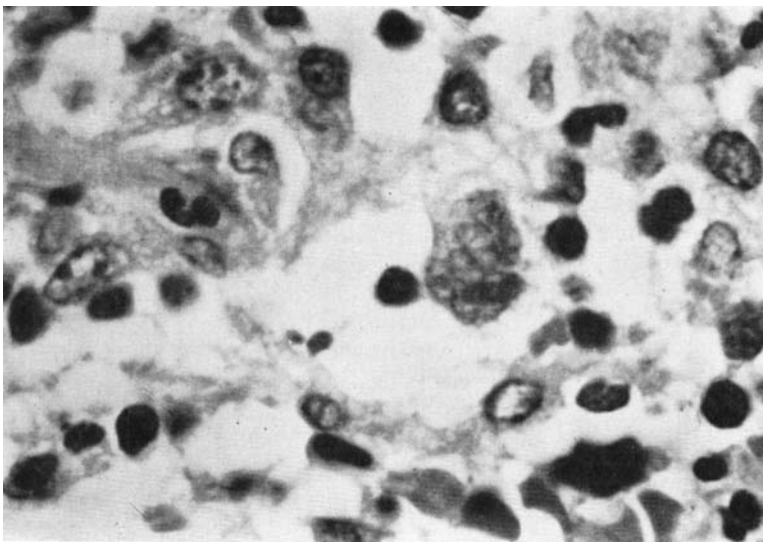

FIG. 9. Same as Fig. 8, showing the Sternberg-Reed cell at high magnification (H and E, ×1,020).

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