The American Journal of Surgical Pathology
Volume 7 · Number 2
March 1983

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Interfollicular Hodgkin's disease

ABSTRACT An unusual pattern of focal involvement of lymph nodes by Hodgkin's disease is described which we have named "interfollicular Hodgkin's disease." It is characterized by florid reactive follicular hyperplasia which overshadows involvement of the interfollicular zones by Hodgkin's disease. The pattern can be mistakenly diagnosed as one of the many causes of reactive follicular hyperplasia. The seven cases studied did not appear to differ clinically from other more recognizable forms of Hodgkin's disease. The importance of this pattern of lymph node involvement by Hodgkin's disease rests on its misdiagnosis as a benign lesion and not on any unusual clinical features.

Am J Surg Pathol 7: 145–149, 1983.

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INTRODUCTION

For several years, we have recognized an unusual pattern of Hodgkin's disease in lymph nodes that we have termed "interfollicular Hodgkin's disease." It is characterized by striking reactive follicular hyperplasia masking interfollicular involvement by Hodgkin's disease, and it may be misinterpreted as reactive follicular hyperplasia. This morphologic variant has received relatively little attention in the literature, but was recognized by Lukes[4] as a form of focal involvement of lymph nodes by Hodgkin's disease. We have selected seven cases which illustrate its most florid state.

MATERIALS AND METHODS

All cases of Hodgkin's disease indexed between January 1969 and December 1979 in the Laboratory of Surgical Pathology, Stanford University Medical Center, in which an interfollicular pattern had been recognized were reviewed. These included cases with any of the following diagnoses: "interfollicular Hodgkin's disease," "Hodgkin's disease, not otherwise specified," "Hodgkin's disease, unclassified," and "reactive follicular hyperplasia with features suggestive of Hodgkin's disease." Fifty-five cases were identified in this manner and included patients hospitalized at Stanford as well as cases that had been sent to one of us (RFD) in consultation. Six of the cases had been previously identified in a recently reported clinicopathologic study of 659 patients with Hodgkin's disease.[1] Cases selected for study showed the following features: 1) a low-

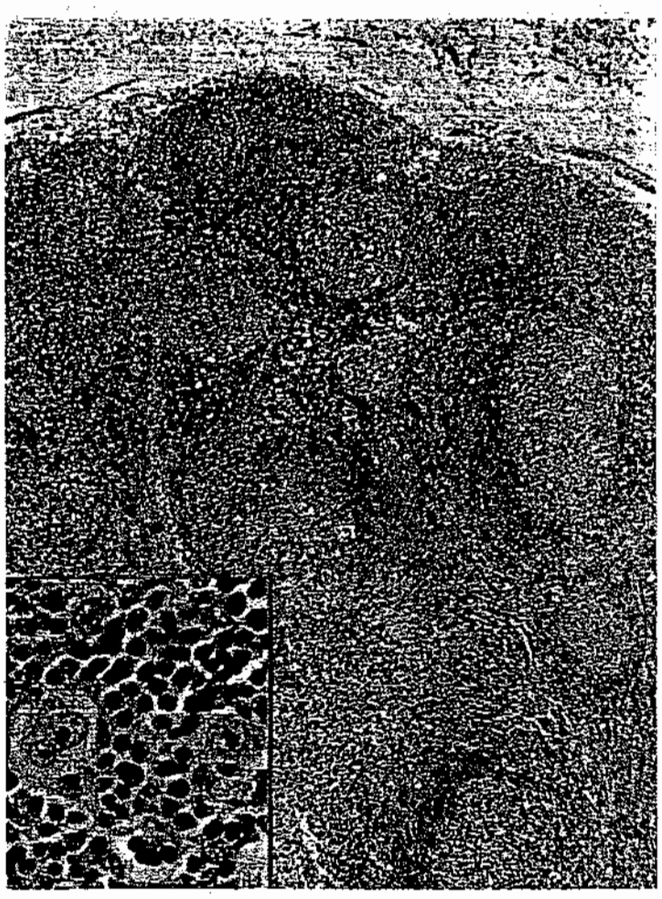

FIGURE 1
Interfollicular Hodgkin's disease. There is prominent reactive follicular hyperplasia in cortex and medulla. Inset from interfollicular zone shows Hodgkin's cells, small mature lymphocytes, and plasma cells.

power (scanning objective) view showing reactive follicular hyperplasia as the dominant feature, and 2) an interfollicular stroma showing features diagnostic of Hodgkin's disease. All patients had been previously untreated.

RESULTS

Seven cases fulfilled our criteria for interfollicular Hodgkin's disease. The remaining 48 were excluded for the following reasons: 1) nodules of easily recognizable Hodgkin's disease overshadowed adjacent reactive follicular hyperplasia; 2) the lymph node failed to show florid reactive follicular hyperplasia with prominent germinal centers.

In the seven cases accepted, follicles with prominent germinal centers dominated the appearance at scanning power (Fig. 1). The interfollicular zones contained an admixture of cells comprising varying proportions of small, round, mature lymphocytes, eosinophils, plasma cells, and epithelioid histiocytes. Diagnostic Reed-Sternberg cells and mononuclear variants thereof were interspersed (Fig. 1 *inset*). The number of diagnostic Reed-Sternberg cells varied; in three cases, they were scarce and a meticulous search was required to identify them, while in three others, they could readily be found. In two instances, clusters of epithelioid histiocytes were seen in interfollicular zones occasionally in proximity to lymphoid follicles reminiscent of toxoplasmic lymphadenitis.[2,3] Plasma cells were prominent in the biopsies of two patients; these cases had initially been confused with the plasma cell variant of giant

TABLE 1.

Interfollicular Hodgkin's disease

Case No.	Age	Sex	Site of Original Biopsy	Staging Laparotomy	Clinical Stage (Ann Arbor)	Pathologic Stage	Therapy	Length of Follow-up Period	Current Physical Status
1	60	F	Supraclavicular lymph node	Mixed cellularity HD with involvement of spleen, bone marrow, periaortic lymph nodes.	IIIB	IVB	Localized radio- and chemotherapy	4 yrs.	Dead of active Hodgkin's disease
2	55	M	Left cervical lymph node	Not performed	IB	—	Mantle irradiation	7 yrs.	Alive and well, NED[a]
3	13	M	Cervical lymph node	Not performed	IIIB	—	Mantle and inverted-Y irradiation, multiple agent chemotherapy	18 yrs.	Alive and well, NED
4	55	F	Right cervical lymph node	Mixed cellularity HD with involvement of spleen bone marrow, liver	IVA	IVA	Mantle and inverted-Y irradiation, multiple agent chemotherapy	3 yrs.	NED
5	20	M	Right supraclavicular lymph node	Negative	IA	IA	Mantle irradiation	6 yrs.	NED
6	40	M	Right cervical lymph node		(No follow-up)				
7	37	M	Left axilla		(No follow-up)				

[a] NED = No evidence of disease.

lymph node hyperplasia. Two cases showed prominent capsular sclerosis with broad collagenous bands, extending irregularly into the lymph node parenchyma without nodule formation. Increased vascularity of the interfollicular stroma was present in all seven cases. Necrosis was not seen. In general, the variation in the cellular composition of the interfollicular stroma paralleled that seen in the histologic subtypes of Hodgkin's disease as defined by the Lukes and Butler classification.[6]

The clinical findings, therapy, and available follow-up data are presented in Table 1.

DISCUSSION

Pathologists are reluctant to diagnose a lesion whose morphologic appearance is unfamiliar to them; the purpose of our report is to draw attention to an unusual pattern of Hodgkin's disease which we have termed "interfollicular Hodgkin's disease." This morphologic variant was not included as a distinct histologic subtype in either the Lukes and Butler or Rye classifications for Hodgkin's disease[5,6] and that, plus its rarity, probably accounts for the general lack of familiarity with it.

Interfollicular Hodgkin's disease can be confused with reactive follicular hyperplasia, well-known causes of which include toxoplasmic lymphadenitis, infectious mononucleosis, viral lymphadenitis, rheumatoid arthritis, and giant lymph node hyperplasia ("Castleman's disease").[2] Some degree of reactive follicular hyperplasia is frequent in lymph nodes involved by Hodgkin's disease, and interfollicular Hodgkin's disease represents the extreme example thereof. Reed–Sternberg cells must be distinguished from immunoblasts which may sometimes appear binucleate in the stroma of antigenically stimulated lymph nodes. The diagnosis of interfollicular Hodgkin's disease is facilitated by

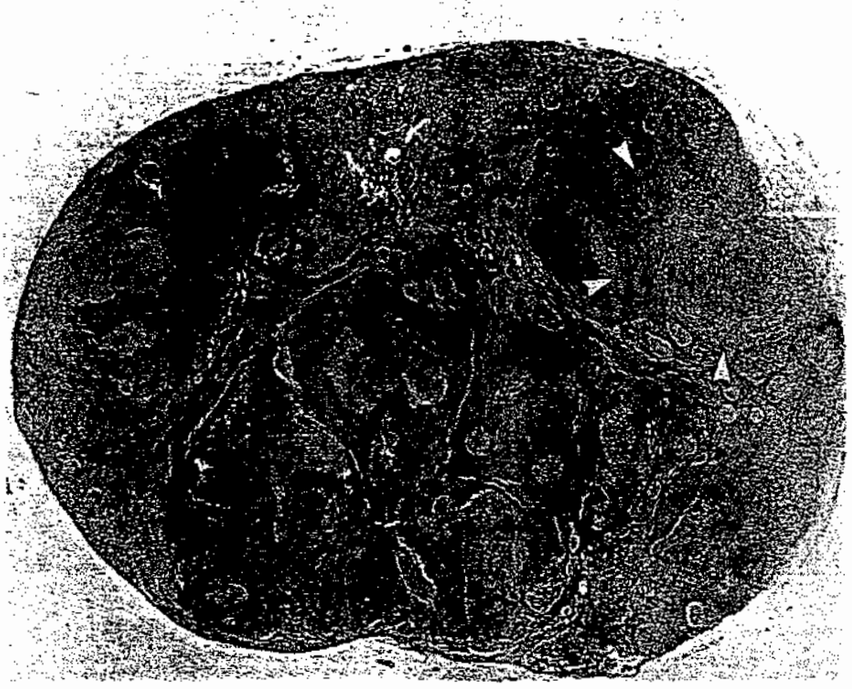

FIGURE 2
Lymph node showing interfollicular Hodgkin's disease occupying most of its volume. However, note small focus of nodular sclerosing Hodgkin's disease in upper right corner (arrowheads).

awareness of the pattern and by careful evaluation of any lymph node showing reactive follicular hyperplasia.

Lukes recognized this pattern of involvement when he pointed out that "small foci of involvement, whether single or multiple are usually situated near the corticomedullary junction and unrelated to sinusoids."[4] We agree with Lukes that interfollicular Hodgkin's disease represents a peculiar form of focal involvement of lymph nodes and that it does not constitute a new entity.

Lukes emphasized that lymph nodes with Hodgkin's disease lacking typical features of lymphocyte predominance, nodular sclerosis, or lymphocyte depletion should be placed in the "mixed cellularity" category. Neither the original Lukes and Butler classification nor the Rye modification thereof specifically recognized interfollicular Hodgkin's disease, which must then be arbitrarily included within the mixed cellularity subtype. We do not consider this approach entirely appropriate. We have encountered a number of examples of interfollicular Hodgkin's disease in which other nodes an interfollicular pattern in a node with nodular sclerosis focally present at one pole (Fig. 2).

By our criteria, interfollicular Hodgkin's disease is rare. From the limited follow-up data and the small number of cases involved, it does not appear to differ significantly in its clinical behavior from other subtypes of Hodgkin's disease. Colby et al. found that the interfollicular pattern, although defined less rigidly than in this study, had no prognostic significance.[1]

Poppema et al.[7] have recently called attention to the association of the nodular L and H form of lymphocytic predominant Hodgkin's disease with progressive transformation of germinal centers. They speculated that progressively transformed germinal centers may be the precursor to this form of Hodgkin's disease. We have made similar observations and find this a very intriguing, although as yet unproved, hypothesis. The problem of distinction between the nodular L and H form of Hodgkin's disease and progressively transformed germinal centers does not arise in the context of interfollicular Hodgkin's disease. In the latter, the

Recognition of the interfollicular pattern of Hodgkin's disease in lymph nodes is important so that unnecessary delays in diagnosis and therapy of a potentially curable disease may be avoided. □

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Acknowledgments

The authors are grateful for the secretarial assistance of Ms. Margaret Beers and the photographic assistance of Mr. Philip Horne.

This work was supported in part by Grants CA05858-21 and CA21555-05 from the National Cancer Institute and National Institutes of Health, Bethesda, Maryland.

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