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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 termed "interfollicular Hodgkin's disease." It is characterized by florid reactive follicular hyperplasia which superimposes involvement of the interfollicular areas by Hodgkin's disease. The pattern can be readily distinguished as one of the more common reactive follicular hyperplasias. The seven cases studied did not appear to differ clinically from other more recognizable forms of Hodgkin's disease. The superposition of this pattern of lymph node involvement by Hodgkin's disease makes it misleading as a benign lesion and not as an unusual clinical feature.


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 making 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 Dukes and Pappenheimer as a form of focal involvement of lymph nodes by Hodgkin's disease. We have selected seven cases which illustrate its varied clinical state.

MATERIALS AND METHODS

All cases of Hodgkin's disease indexed between January 1960 and December 1975 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) for consultation. Six of the cases had been previously identified in a recently reported clinicopathologic study of 159 patients with Hodgkin's disease.1 Cases selected for study showed the following features: 1) a low-
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 recog-
nizable 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 prom-
inent 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 in-
terfollicular zones occasionally in proximity to
lymphoid follicles reminiscent of toxoplasmosis lympho-
adenitis.15–17 Plasma cells were prominent in the
biopsies of two patients; these cases had initially
been confused with the plasma cell variant of giant

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Site of Original Tumor</th>
<th>Stage on Presentation</th>
<th>Chemotherapy</th>
<th>Pathologic Stage</th>
<th>Therapy</th>
<th>Length of Follow-up</th>
<th>Current Physical Status</th>
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</thead>
<tbody>
<tr>
<td>1 60</td>
<td>F</td>
<td>F</td>
<td>Supraclavicular lymph node</td>
<td>Mixed cellularity /D with involvement of spleen, bone marrow, periaortic lymph nodes.</td>
<td>IAIB</td>
<td>IVA</td>
<td>Localized radio- and chemotherapy</td>
<td>4 yrs.</td>
<td>Died of active Hodgkin's disease</td>
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<tr>
<td>2 55</td>
<td>M</td>
<td>L</td>
<td>Left cervical lymph node</td>
<td>Not performed</td>
<td>IB</td>
<td>—</td>
<td>Mantle irradiation</td>
<td>7 yrs.</td>
<td>Alive and well, NED</td>
</tr>
<tr>
<td>3 13</td>
<td>M</td>
<td>C</td>
<td>Cervical lymph node</td>
<td>Not performed</td>
<td>IB</td>
<td>—</td>
<td>Mantle and inverted-Y irradiation, multiagent chemotherapy</td>
<td>18 yrs.</td>
<td>Alive and well, NED</td>
</tr>
<tr>
<td>4 55</td>
<td>F</td>
<td>R</td>
<td>Right cervical lymph node</td>
<td>Mixed cellularity /D with involvement of spleen, bone marrow, liver, and lung</td>
<td>IVA</td>
<td>IVA</td>
<td>Mantle and inverted-Y irradiation, multiagent chemotherapy</td>
<td>3 yrs.</td>
<td>NED</td>
</tr>
<tr>
<td>5 20</td>
<td>M</td>
<td>R</td>
<td>Right supraclavicular lymph node</td>
<td>(No follow-up)</td>
<td>IA</td>
<td>IA</td>
<td>Mantle irradiation</td>
<td>6 yrs.</td>
<td>NED</td>
</tr>
<tr>
<td>6 46</td>
<td>M</td>
<td>R</td>
<td>Right cervical lymph node</td>
<td>(No follow-up)</td>
<td>(No follow-up)</td>
<td>(No follow-up)</td>
<td>(No follow-up)</td>
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</tr>
<tr>
<td>7 57</td>
<td>M</td>
<td>L</td>
<td>Left axilla</td>
<td>(No follow-up)</td>
<td>(No follow-up)</td>
<td>(No follow-up)</td>
<td>(No follow-up)</td>
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</tbody>
</table>

* 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 nodal invasion. Increased vascularity of the interfollicular stroma was present in all seven cases. Necrosis was present 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.48

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.34 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 ("Castaneda's disease").5 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 hibernating in the stroma of antigenically stimulated lymph nodes. The diagnosis of interfollicular Hodgkin's disease is facilitated by

Vol. 7 No. 2 March 1983
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 inserted near the cortical-medullary junction and unrelated to sinuoids." We agree with Lukes that interfollicular Hodgkin's disease represents a peculiar form of foci of 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 lymphocytic predominance, nodular sclerosis, or lymphocytic depletion should be placed in the "mixed cellularity" category. Neither the original Lukes and Butler classification nor the Fára 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

\[ \text{Figure 2: Lymph node showing interfollicular Hodgkin's disease occupying most of the sinus node. However, note small foci of nodular sclerosis in upper right corner (arrow).} \]

an interfollicular pattern in a node with nodular sclerosis finally 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.

Popper et al. 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 very intriguing, although as yet unproven, hypothesis. The problem of distinction between the nodular L and H form of Hodgkin's disease and progressively transformed germinal centers is deBout's 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.

References


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