Comparison of Fascin Expression in Anaplastic Large Cell Lymphoma and Hodgkin Disease

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Abstract

Diagnostic difficulties sometimes arise in distinguishing anaplastic large cell lymphoma (ALCL) from Hodgkin disease (HD), especially the syncytial variant. Study of the biologic features of diagnostic Reed-Sternberg cells in HD, in search of specific markers for Reed-Sternberg cells, has suggested fascin as a relatively specific and sensitive marker. We studied the frequency of fascin expression in 30 ALCLs and 34 cases of classic HD, including 17 cases of the syncytial variant. Staining with CD30 and anaplastic lymphoma kinase (ALK)-1 also was performed in all cases. All ALCL and HD cases showed membranous and Golgi zone CD30 positivity. Fascin stained all HD cases but also stained 67% (20/30) of the ALCLs in a cytoplasmic pattern. Fascin positivity was observed in 59% (10/17) of T-cell ALCLs and 77% (10/13) of null-cell ALCLs; ALK-1–positive ALCLs, regardless of origin, were usually fascin-positive (91% [10/11]). In conclusion, fascin shows strong positivity in all cases of classic HD but also is positive in the majority of ALCLs, including ALK-1–positive and ALK-1–negative cases. Positive staining for fascin is not useful for distinguishing ALCL from HD. In some cases, fascin negativity may help rule out classic HD.

Anaplastic large cell lymphoma (ALCL) initially was defined as a CD30+ large cell lymphoma with characteristic morphologic features and a propensity to involve both nodal and extranodal sites.1 After the original description of ALCL, it was recognized that ALCL varies in its histologic spectrum, immunophenotype, and clinical manifestations. Although there is accumulating evidence that ALCL and Hodgkin disease (HD) are biologically distinct entities, there is considerable morphologic and immunological overlap between these 2 diseases.2,3 During the late 1980s, the t(2;5) chromosomal translocation was identified and found to be associated with ALCL.4-6 As a consequence of this translocation, the anaplastic lymphoma kinase (ALK) gene on chromosome 2 comes under the control of the nucleophosmin (NPM) gene promoter on chromosome 5. This translocation induces permanent and ubiquitous transcription of the NPM-ALK hybrid gene by the ALCL cells, resulting in the production of a hybrid NPM-ALK protein. Interphase fluorescent in situ hybridization (FISH) can be used for detection of the t(2;5) in ALCL.7 The ALK-1 monoclonal antibody is used to detect the abnormal NPM-ALK protein.8 However, ALK-1 is expressed by only approximately 50% of ALCLs.9-11 Despite advances in immunohistochemical analysis and molecular diagnostics, there are persistent difficulties in distinguishing between ALCL and HD in many cases.

Fascin is an actin-bundling protein that was first isolated from cytoplasmic extracts of sea urchin eggs.12 In 1994, the gene for human fascin was cloned.13 Subsequent work showed that fascin was involved in the formation of dendritic processes14,15 and demonstrated that fascin expression in germinal center dendritic cells was altered in the neoplastic
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Follicles of follicular B-cell lymphomas and also in follicular hyperplasia. An HD cell line, KM-H2, was found to show biphenotypic features of dendritic cells and B cells, and some investigators suggested that fascin might be used as a specific marker for Reed-Sternberg (RS) cells. One study found that RS cells and RS variants showed fascin positivity in all classic HD cases, but that the “popcorn” or “L&H” (lymphocytic and histiocytic) cells of lymphocyte predominant HD were negative for fascin. Only 15% of non-Hodgkin lymphoma cases were positive for fascin, but 75% of the ALCL cases (12/16) showed weak fascin positivity. A later study reported strong fascin positivity in 2 nodal ALCLs.

To date, no large serial study has compared fascin expression in ALCL and HD, and the specificity of fascin for RS cells in classic HD and the clinical usefulness of fascin immunohistochemical staining have not been determined. To determine the frequency and specificity of fascin positivity in ALCL and HD, we studied a large number of consecutive cases of ALCL and HD for fascin expression and for expression of ALK-1. A subset of the ALK-1– and fascin-positive ALCL cases also were tested for the t(2;5) by the FISH method.

Materials and Methods

Archival tissues were retrieved from the files of the Hematopathology Division, Department of Pathology, at Indiana University, Indianapolis, and Oregon Health & Science University, Portland. Thirty cases of ALCL and 34 cases of HD were included. Tissues were fixed in 10% formalin or B-5 solution. All cases were stained with the CD3, CD20, CD30, fascin, and ALK-1 antibodies (DAKO, Carpinteria, CA) by an avidin-biotin complex method and were diagnosed according to standard morphologic and immunological criteria by 2 or more hematopathologists (G.F., P.K., R.S.N., R.M.B.).

Interphase FISH Analysis

Four randomly selected ALK-1–positive ALCL cases were used. Five-micrometer-thick sections from paraffin-embedded tissue were used. Interphase FISH analysis was performed by a standard technique in a referral cytogenetic laboratory. Details of the method are available in the article by Kimberley et al.

Cases

A total of 30 ALCL cases were evaluated, including 17 T-cell and 13 null-cell types. The ages of patients with ALCL ranged from 7 to 79 years (mean, 37 years). There was a male predominance (M/F ratio, 1.5:1). The ALCL lesions were found at various body sites, including nodal and extranodal, above and below the diaphragm. The 34 HD cases included 17 syncytial variants of nodular sclerosis HD, 12 typical nodular sclerosis HD cases, and 5 mixed cellularity HD subtypes. Most patients were young, with a mean age of 35 years. The majority of lesions were in nodal sites above the diaphragm. A slight male predominance (M/F ratio, 1.3:1) also was observed in the patients with HD. Additional clinical information is given in Table 1.

Statistics

To determine the significance of differences between fascin expression in ALCL and in the classic HD, the Pearson chi-square test was used.

Results

The representative morphologic features of ALCL and syncytial variant HD are shown in Image 1A and Image 1B. All ALCL and all HD cases showed CD30 membranous and Golgi zone positivity Image 1C and Image 1D. Of 30 ALCLs, 17 cases were CD3+, and 20 cases showed strong cytoplasmic staining for fascin in tumor cells Image 1E. None of the cases showed positive staining for CD30. All of the HD cases revealed cytoplasmic staining for fascin in the RS cells Image 1F. 4 HD cases had CD20 reactivity, and none showed CD3 or ALK-1 positivity.

The frequency of fascin positivity was compared between T-cell and null-cell ALCLs: 10 (59%) of 17 T-cell ALCLs and 10 (77%) of 13 null-cell ALCLs showed fascin positivity.

Table 1

Clinical Information for Patients With Anaplastic Large Cell Lymphoma and Hodgkin Disease

<table>
<thead>
<tr>
<th>Anaplastic Large Cell Lymphoma</th>
<th>Hodgkin Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Cell (n = 17)</td>
<td>Nodular Sclerosis (n = 12)</td>
</tr>
<tr>
<td>Mean age (range) (y)</td>
<td>41 (9-78)</td>
</tr>
<tr>
<td>M/F ratio</td>
<td>2.4:1</td>
</tr>
<tr>
<td>Disease sites and number of cases</td>
<td>Lymph node, 11; skin, 2; mediastinum, 1; abdomen, 1; liver, 1; bone marrow, 1</td>
</tr>
</tbody>
</table>

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There was no statistical difference in fascin expression between the 2 ALCL subtypes ($P > .05$).

In this study, 11 (37%) of 30 ALCLs were positive for ALK-1 [Image 1G], while none of the HD cases were positive [Image 1H]. The mean age of patients with ALK-1–positive ALCL was 28 years. In contrast, the patients with ALK-1–negative ALCL were older (mean age, 51 years). When divided into 3 age groups (younger than 20 years, 20-40 years, and older than 40 years), the incidence of ALK-1–positive cases was highest in the youngest group [Figure 1]. The analysis of fascin expression in ALK-1–positive and ALK-1–negative ALCL cases showed that 10 (91%) of 11 ALK-1–positive and 9 (47%) of 19 ALK-1–negative ALCL cases stained for fascin [Figure 2].

Four ALK-1– and fascin-positive ALCL cases were tested for t(2;5) by interphase FISH analysis. All of the cases showed an abnormal chromosome 2, consistent with the presence of an ALK gene rearrangement.

**Discussion**

We studied 30 cases of ALCL and 34 of HD to determine the frequency of fascin expression and to evaluate the clinical usefulness of fascin staining in conjunction with CD30 and ALK-1 staining patterns. In our study, ALK-1 activity was seen in only 37% of all ALCL cases (11/30). This low incidence of ALK-1 positivity may be due to the...
older age of our patient population. The percentages of ALK-1–positive ALCLs in different age groups are in the ranges given in previous reports.\textsuperscript{21-23}

In the present study, fascin was detected in the majority but not all ALCL cases (20/30 [67%]); the ALK-1–positive ALCL cases were more frequently fascin positive.


**Table 2**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CD30</th>
<th>ALK-1</th>
<th>Fascin</th>
<th>CD3</th>
<th>CD20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular sclerosis HD (n = 12)</td>
<td>12 (100)</td>
<td>0 (0)</td>
<td>12 (100)</td>
<td>0 (0)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Nodular sclerosis HD, syncytial (n = 17)</td>
<td>17 (100)</td>
<td>0 (0)</td>
<td>17 (100)</td>
<td>0 (0)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Mixed cellularity HD (n = 5)</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>5 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ALCL, T-cell (n = 17)</td>
<td>17 (100)</td>
<td>7 (41)</td>
<td>10 (59)</td>
<td>17 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ALCL, null-cell (n = 13)</td>
<td>13 (100)</td>
<td>3 (23)</td>
<td>10 (77)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase.
\textsuperscript{*} Data are given as number (percentage) of positive cases.
(10/11 [91%]) than were the ALK-1–negative cases (9/19 [47%]). The difference in fascin expression between the T-cell and null-cell subtypes of ALCL was not statistically significant ($P > .05$). Fascin always is positive in the RS cells of classic HD, but it was not completely specific for RS cells in our study. We also saw fascin staining in endothelial cells, dendritic cells, and histiocytes. Staining of these cell types has been reported before. Fascin also has been reported to be positive in Epstein-Barr virus–positive B cells.

Fascin clearly is not a specific marker for HD. If staining is positive, it is not helpful in distinguishing ALCL from HD. However, the lack of fascin expression may be helpful for excluding the diagnosis of HD. Thus, in diagnostically difficult cases of ALCL and HD, the addition of fascin to the immunohistochemical panel may provide useful corroborative information in a subset of cases.

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References


