Immunophenotypic Analysis of CD103+ B-Lymphoproliferative Disorders

Hairy Cell Leukemia and Its Mimics

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Abstract

CD103 is characteristically expressed in hairy cell leukemia (HCL), a B-lymphoproliferative disorder highly responsive to treatment with purine analogs. Other CD103+ diseases are rare and do not respond well to the same therapy, including HCL variant (HCLv) and splenic marginal zone B-cell lymphoma (SMZL) variants. We analyzed 215 cases of CD103+ B-lymphoproliferative disorders to further delineate their immunophenotypic features. Flow cytometric analysis revealed that 78.6% of all cases expressed CD25 and CD103, characteristic of classical HCL. Cases analyzed immunohistochemically were also invariably positive for annexin-A1; a subset coexpressed CD10 (33/169 [19.5%]) or BCL1 (26/65 [39.9%]). In contrast, 21.4% of cases lacked CD25, a subset of which was analyzed and was invariably negative for annexin-A1, CD10, and BCL1. The CD25−/− cases had variable morphologic features ranging from HCLv and SMZL to prolymphocytic leukemia and diffuse large B-cell lymphoma. Clinically, patients with CD25− disease tended to be older (P = .001), typically had leukocytosis (P = .014), and did not respond well to cladribine or pentostatin. We suggest categorizing CD103+ B-lymphoproliferative disorders into 2 groups. While HCL coexpresses CD25 and annexin-A1, diseases lacking CD25 and annexin-A1 behave clinically differently and can be separated from HCL on diagnosis.

CD103 is a cell surface glycoprotein of the integrin β7 family, initially discovered by raising a monoclonal antibody (B-ly7) directly against hairy cell leukemia (HCL). Since its discovery, CD103 has been widely used for the diagnosis of HCL. Despite rare exceptions in the recent literature, CD103 has been detected, together with CD25, in every case of HCL in virtually all previous large studies using flow cytometry. In contrast, CD103 is not ordinarily detected in other types of B-lymphoproliferative disorders except for rare cases of splenic marginal zone B-cell lymphoma (SMZL) and diffuse large B-cell lymphomas (DLBCL). Only rare entities are known to be frequently CD103+, namely HCL variant (HCLv) and splenic red pulp lymphoma with villous lymphocytes (SRPL). Consequently, expression of CD103 has been considered one of the most useful diagnostic criteria for HCL.

HCL is a rare, chronic B-lymphoproliferative disorder characterized by distinctive clinical manifestations and peculiar cytomorphologic features. In recent years, treatment with the purine analogs cladribine and pentostatin has achieved complete response rates of 79% to 95%, overall response rates of 96% to 100%, and 5-year disease-free survival rates of greater than 88%. Other rare diseases (eg, HCLv) with frequent CD103 expression and hairy cell–like morphologic features do not respond well to purine analogs. Therefore, an accurate diagnostic assessment helps to better stratify patients who will benefit from highly effective therapy and to avoid unnecessary toxic effects, especially in the light of a recent concern that patients with HCL might be at an increased risk of secondary malignancies.
Coexpression of CD25 and CD103 identified by flow cytometry has been the most reliable finding at diagnosis. A cytochemical stain for tartrate-resistant acid phosphatase may improve diagnostic accuracy. However, expression of tartrate-resistant acid phosphatase based on immunohistochemical detection seems to be much less specific and has been found in various subtypes of B-cell lymphoma. Hounieu et al discovered that DBA.44 was a sensitive antibody for diagnosis of HCL by immunohistochemical analysis, although it also lacks sufficient specificity. The variable immunophenotypes described in the literature, particularly the lack of CD25 or surface immunoglobulin, have resulted in a few proposed variants of HCL. The detection of antigens typical of other types of B-cell lymphoma, such as BCL1 and CD10, in HCL, has made the diagnosis more challenging. Recently, the immunohistochemical staining of annexin-A1 has been shown to reliably distinguish HCL from other B-cell lymphomas, including SMZL and HCLv. However, annexin-A1 is also strongly expressed in myeloid cells and, thus, cannot be easily applied for low-level marrow involvement by HCL.

We have continuously observed that HCL and HCLv are often used as interchangeable terms in practice because of their coexpression of CD103. Our study is aimed at updating the immunophenotype of all CD103+ B-lymphoproliferative disorders. To this end, we characterized 215 cases of CD103+ B-lymphoproliferative disorders by flow cytometry and immunohistochemical analysis in an attempt to provide further aid in diagnosis and subsequent patient care.

**Materials and Methods**

A total of 215 consecutive cases of CD103+ B-lymphoproliferative disorders in a 3-year period were analyzed for their immunophenotypic profiles. In all cases, a final diagnosis was established by immunophenotyping in conjunction with the available clinical impression and cytomorphologic and histologic findings. The specimens consisted of bone marrow (69.3%), peripheral blood (27.0%), spleen (1.9%), and lymph nodes (1.9%). The percentage of clonal B cells in the specimens ranged from 8% to 90% (median, 20%). The diagnosis in all cases with fewer than 5% of leukemic cells by initial flow cytometric analysis, typically in peripheral blood specimens, was further confirmed by subsequent evaluation of a bone marrow biopsy specimen, which always had more extensive involvement.

We performed 4-color flow cytometry according to standard procedures. The details of the antibody combinations and the method for direct immunofluorescent staining have been previously published. Antibodies in the routine lymphoma or leukemia panels (Beckman Coulter, Miami, FL) included CD10, CD11c, CD19, CD20, CD22, CD23, CD38, κ, λ (B-cell antigens), CD2, CD3, CD4, CD5, CD7, CD8, and CD56 (T- and NK-cell antigens). Staining for CD25 (clone M-A251, BD Biosciences Pharmingen, San Jose, CA) and CD103 (clone B-ly7, IQ Product, Groningen, the Netherlands) was performed as a part of the routine panel for the lymphoma workup during the first year of the study period but was later used only when HCL was suspected. A minimum of 10,000 total events was required for each analysis; 20,000 events were routinely acquired. Data were analyzed on the FACSCalibur with CellQuest Pro software (BD Biosciences, San Jose, CA). The expression levels of individual antigens were categorized as strong (bright), moderate, and weak (dim) based on the fluorescence intensity over isotype controls of greater than 1.5 logs, between 1 and 1.5 logs, and below 1 log, respectively.

Immunohistochemical staining was performed by using a labeled streptavidin-biotin (LSAB) procedure in a TechMate 500 automatic immunostainer (Ventana Medical Systems, Tucson, AZ) as described previously. Only a subset of cases had biopsy tissue for immunohistochemical study, and only immunohistochemical results for antigens that were not analyzed by flow cytometry will be discussed. These included BCL1 (clone DCS-6, NeoMarkers, Fremont, CA), BCL-2 (clone 124, DAKO, Carpinteria, CA), CD43 (clone L60, DAKO), DBA.44 (DAKO), and annexin-A1 (clone 29, BD Transduction Laboratories, San Jose, CA). Unequivocal nuclear staining was necessary for positive BCL1 immunoreactivity. Staining of annexin-A1 (antibody titer, 1:100) was performed in a subset of cases in parallel with CD20 staining in each case.

**Results**

**Immunophenotypic Analysis of CD103+ B-Lymphoproliferative Disorders Identified Two Major Groups With Distinct Features**

All 215 cases displayed strong expression of CD11c, CD20, and CD22, a hallmark phenotypic profile for CD103+ diseases. In addition, they typically lacked expression of CD5, CD23, and CD38, which were detected in only a subset of cells by flow cytometry, in 2.3%, 4.7%, and 8.8% of cases, respectively. Strong coexpression of CD5 and CD23, characteristic of chronic lymphocytic leukemia, was never observed. The overall results of immunophenotype analysis by flow cytometry are summarized in Table I.

Based on flow cytometry, 169 cases (78.6%) were classical HCL with coexpression of CD25. These cases...
Consistently presented a distinct lymphoid population in the monocyte gate Image 1A on analysis of CD45 vs side scatter and forward scatter vs side scatter. The remaining 46 cases (21.4%) lacked CD25 and were typically composed of small B cells in the normal lymphocyte gate Image 1B. Three cases of CD103+ DLBCL and prolymphocytic leukemia had immunophenotypic features identical to other CD25− cases except for increased forward scatter, correlating to increased cell size.

Significant differences were observed between the CD25+ HCL and CD25− cases. Classical HCL displayed homogeneous expression of CD10 in 19.5% (33/169) of the cases at expression levels comparable to those of follicular lymphoma Image 1B. In contrast, none of the CD25− cases had detectable CD10 (P = .001). HCL was slightly λ predominant (κ/λ, 0.9:1), whereas the CD25− cases displayed more frequent surface κ expression (κ/λ, 1.6:1) and tended to have more frequent low-level or undetectable surface light chain (20.9% [9/43]) compared with classical HCL (4.1% [7/169]) (P = .02).

Based on immunohistochemical results Table 2, all 79 tested CD103+ cases expressed DBA.44 and BCL-2; none of the 79 had detectable CD43. All 28 tested classical HCL cases were invariably positive for annexin-A1. About 36.9% of classical HCL cases (24/65) also had overexpression of BCL1 (Image 2), although the intensity of BCL1 staining was highly variable. In contrast, expression of annexin-A1 was never detected in any of the stained CD25− cases, nor was BCL1 (0/14) (P = .04).

It is worth noting that, as a whole, the expression of CD20, CD22, and CD11c was distinctively brighter in CD103+ B-lymphoproliferative disorders than in normal B cells and most other subtypes of B-lymphoproliferative disorders. This profile often allowed detection of a very small number of abnormal cells (as few as 0.1% of total cells) in a polyclonal background Image 1C during screening, a feature useful for monitoring low-level disease.

CD103+ B−lymphoproliferative Disorders With or Without CD25 Differ in Morphologic Features

Cytologically, classical HCL cells were medium-sized with eccentric nuclei, reticulated chromatin, ruffled cytoplasmic borders, and irregular surface projections (Image 2). The presence of prominent nucleoli was also noted in a few cases. In contrast, the morphologic features of CD25− cases were more variable. These cells were typically small to medium-sized with more condensed, coarse chromatin and fine cytoplasmic projections. The presence of a prominent nucleolus was noted in at least some cells in all cases, even though cells with varying morphologic features coexisted in most cases Image 3. Histologically, classical HCL characteristically displayed an extensive interstitial infiltrate in narrow trephine biopsy specimens without aggregation. The leukemic cells typically displayed abundant pale cytoplasm in a “fried egg” appearance (Image 2). In contrast, the cases lacking CD25 displayed a patchy infiltrate or distinct clusters of small lymphocytes in the marrow (9/14 cases), even though they were often inconspicuous on the H&E-stained section (Image 3). The infiltrate often displayed an exclusive intrasinusoidal infiltration best seen on CD20 and CD34 staining (6/14 cases).

The CD25− group included 1 case with large cell and 2 cases with large prolymphocytic histologic features in tissue sections (Image 3). The large B-cell lymphoma was identified in a lymph node biopsy specimen from a patient with a history of HCLv diagnosed 3 years earlier. The immunophenotypic profile of the large cells was identical to that at the initial diagnosis of HCLv, suggesting large cell transformation of the initial disease. The neoplastic cells in this case displayed enlarged cell size, irregular nuclear contours, and vesicular chromatin. The other 2 cases manifested as de novo splenic lymphoma, both of which were composed of predominantly prolymphocytes/paraimmunoblasts (2- to 3-fold larger than normal lymphocytes) with a single prominent nucleolus in a diffuse growth pattern effacing architecture.
CD103+ B-Lymphoproliferative Disorders With or Without CD25 Were Correlated With Different Clinical Manifestations

The study included a total of 173 men and 42 women (M/F, 4.2:1). The patients with CD25− disease were significantly older (median, 79 years) than patients with classical HCL (median, 59 years) \((P < .001)\). At diagnosis, they also had leukocytosis and lymphocytosis without monocytopenia, as opposed to pancytopenia, leukopenia \((P < .014)\), and monocytopenia in classical HCL. Of 7 patients with CD25− disease who were treated with a purine analog and had meaningful...
follow-up data available (range, 9-62 months), the complete response (CR) rate was 14% (1/7) and the overall response rate was 57% (4/7). The only patient who achieved CR had a relapse 48 months later but achieved the second CR after additional cladribine therapy. Of the 3 patients who achieved a partial response, 1 subsequently achieved CR with rituximab. One had a partial response to fludarabine plus rituximab on disease progression. The third patient died of the disease
## Table 2: Immunophenotype of CD103+ B-Lymphoproliferative Disorders Analyzed by Immunohistochemical Studies\(^\text{a}\)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>DBA.44 (n = 79)</th>
<th>Annexin-A1 (n = 42)</th>
<th>CD43 (n = 79)</th>
<th>BCL1 (n = 79)</th>
<th>BCL-2 (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD25+</td>
<td>65/65 (100)</td>
<td>28/28 (100)</td>
<td>0/65 (0)</td>
<td>24/65 (37)</td>
<td>65/65 (100)</td>
</tr>
<tr>
<td>CD25-</td>
<td>14/14 (100)</td>
<td>0/14 (0)</td>
<td>0/14 (0)</td>
<td>0/14 (0)</td>
<td>14/14 (100)</td>
</tr>
</tbody>
</table>

\(\text{a}\) Data are given as number/total (percentage).

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**Image 3** Morphologic features of CD25−, CD103+ B-lymphoproliferative disorders. **A** and **B**, The neoplastic cells have more condensed chromatin, compared with hairy cell leukemia, and fine cytoplasmic projections. Prominent nucleoli are common. Cells with diverse morphologic features often coexist in a given case (Wright-Giemsa, ×1,000). **C** and **D**, The bone marrow histologic features tend to show lymphoid aggregates or patchy clusters (**C**, H&E, ×400), as highlighted by CD20 staining (**D**, ×400). **E** and **F**, In rare cases, a diffuse large cell proliferation (**E**, lymph node) or overwhelming prolymphocytic features (**F**, spleen) were evident compared with normal small lymphocytes as the internal control (H&E, ×1,000).
Discussion

In this study, we analyzed 215 cases of CD103+ B-lymphoproliferative disorders, including 169 cases characteristic of classical HCL (56 cases per year). The number of the classical HCL cases was equivalent to 2.6% of the adult leukemia cases (56/2,187) and 1.1% of the cases of lymphoproliferative disorders (56/5,189) seen annually at our institution. These numbers are in keeping with the current literature, eg, HCL constituted 2% of all adult leukemia and 1% of lymphoproliferative disorders.

We demonstrated that CD103+ B-lymphoproliferative disorders, as a whole, consistently had a distinct phenotypic profile, ie, bright CD11c, CD20, and CD22. This observation was especially verified by our initial unbiased data when CD103 and CD25 were universally used for all cases of lymphoma workup during the first year of this study. Of all cases, 78.6% were consistent with classical HCL that invariably expresses CD25 and annexin-A1. However, exceedingly rare cases of HCL lacking CD103 expression have been reported in the literature. We have also seen 2 such cases during past years. One was a relapsed HCL and was the only case observed in our institution that exhibited the loss of CD103 during the disease course. The other was a de novo HCL with characteristic morphologic features and clinical manifestations. In both cases, the distinct profile of bright CD11c, CD22, and CD22 provided the initial diagnostic clue, and both cases retained expression of CD25 and annexin-A1. The de novo case was also BCL1+.

The specific expression of annexin-A1 in classical HCL was initially discovered by gene expression profiling. It was subsequently validated to be 100% sensitive and specific for HCL in an immunohistochemical study with 500 cases of B-cell malignancies. In particular, it was positive in all cases of classical HCL and negative in all cases of SMZL and HCL*. Our experience has been in agreement with the published data. However, annexin-A1 is also strongly expressed in normal myeloid cells and, therefore, is best used for HCL with extensive marrow involvement or with extramedullary disease. A parallel CD20 stain should always be performed to distinguish HCL cells from nonlymphoid elements in the marrow. In accordance with gene expression profiling data, HCL cases also exhibited unequivocal BCL1 overexpression detectable by immunohistochemical analysis. The expression level of BCL1 was variable, which may account for the wide range of detection rates in the literature (7%-90%). Nevertheless, expression of BCL1 in HCL is not related to the BCL1 translocation, and its clinical implication is yet to be determined.

Consistent with others who had reported CD10 expression in 10% to 26% of HCL cases, we found expression of CD10 in 19.5% of HCLs. However, it does not seem to have any known clinical impact. In practice, a small or crushed specimen with limited immunophenotyping may give rise to an impression of mantle cell lymphoma (BCL1+) or follicular lymphoma (CD10+). Awareness of the common phenotypic profiles instead of relying on a single antigen should help recognize different entities. Of note, neither t(11;14) nor t(14;18) has been detected in HCL.

Apart from classical HCL, about 21.4% of all CD103+ B-lymphoproliferative disorders lacked CD25, annexin-A1, CD10, and BCL1. This phenotypic profile is identical to most cases of HCLv and SRPL, both of which lack CD123 seen in classical HCL as well.

Table 3

*Summary of Clinical Information for Patients With CD25−, CD103+ Splenic B-Cell Lymphoma, Unclassifiable*

<table>
<thead>
<tr>
<th>Case No./Sex/Age (y)</th>
<th>WBC Count (x 10^3/L)</th>
<th>Lymphocyte Count (%)</th>
<th>Hepatosplenomegaly</th>
<th>Adenopathy</th>
<th>Initial Therapy</th>
<th>Response (mo)</th>
<th>Relapse</th>
<th>Secondary Therapy</th>
<th>Follow-up (mo)</th>
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<tr>
<td>1/M/76</td>
<td>47.8</td>
<td>35</td>
<td>No</td>
<td>No</td>
<td>Cladribine</td>
<td>CR (48)</td>
<td>Yes</td>
<td>Cladribine</td>
<td>NED (14)</td>
</tr>
<tr>
<td>2/M/75</td>
<td>4.9</td>
<td>52</td>
<td>Yes</td>
<td>No</td>
<td>Cladribine</td>
<td>PR (7)</td>
<td>—</td>
<td>Rituximab</td>
<td>NED (13)</td>
</tr>
<tr>
<td>3/M/78</td>
<td>8.7</td>
<td>56</td>
<td>Yes</td>
<td>No</td>
<td>Cladribine</td>
<td>PR (22)</td>
<td>—</td>
<td>Cladribine, rituximab</td>
<td>AW (28)</td>
</tr>
<tr>
<td>4/M/76</td>
<td>26.0</td>
<td>80</td>
<td>Yes</td>
<td>Yes</td>
<td>Pentostatin</td>
<td>PR (6)</td>
<td>—</td>
<td>Pentostatin, rituximab</td>
<td>DOD (10)</td>
</tr>
<tr>
<td>5/F/59</td>
<td>12.0</td>
<td>86</td>
<td>Yes</td>
<td>No</td>
<td>Cladribine</td>
<td>NR</td>
<td>—</td>
<td>None</td>
<td>AW (9)</td>
</tr>
<tr>
<td>6/M/72</td>
<td>14.8</td>
<td>56</td>
<td>Yes</td>
<td>No</td>
<td>Cladribine</td>
<td>NR</td>
<td>—</td>
<td>None</td>
<td>AW (13)</td>
</tr>
<tr>
<td>7/M/73</td>
<td>18.4</td>
<td>84</td>
<td>Yes</td>
<td>No</td>
<td>Cladribine</td>
<td>NR</td>
<td>—</td>
<td>Splenectomy</td>
<td>NED (36)</td>
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<tr>
<td>8/M/74</td>
<td>13.0</td>
<td>67</td>
<td>No</td>
<td>—</td>
<td>Fludarabine</td>
<td>CR (12)</td>
<td>No</td>
<td>—</td>
<td>NED (12)</td>
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<tr>
<td>9/F/82</td>
<td>7.7</td>
<td>43</td>
<td>Yes</td>
<td>No</td>
<td>Rituximab</td>
<td>PR (6)</td>
<td>—</td>
<td>None</td>
<td>AW (6)</td>
</tr>
</tbody>
</table>

AWD, alive with disease; CR, complete response; DOD, died of disease; NED, no evidence of disease; NR, no response; PR, partial response.

According to Swerdlow et al, values for the WBC count are given in Système International (SI) units; to convert to conventional units (µL), divide by 0.001; lymphocyte values are given in conventional units; to convert to SI units (proportion of 1.0), multiply by 0.01.
Earlier studies also revealed the phenotypic distinctions between HCL and HCLv and similarities between HCLv and SMZL. In a study using a scoring system with 4 antigens (CD11c, CD25, CD103, and HC2) each counting as 1 point, 98% of classical HCLs scored 3 or 4 points and none scored 0 or 1. In contrast, 88% of HCLv and 77% of SMZL scored 1 or 2 points, but none scored 3 or 4. The tendency to display low levels of surface immunoglobulin in a subset of CD25– cases is also reminiscent of the so-called Japanese variant of HCL. Based on the multiple antigen profiles further supported by recent data for gene expression profiling (eg, annexin-A1 and BCL1), it seems that HCL is sufficiently different from other CD103+ B-lymphoproliferative disorders. On the other hand, CD25– diseases are likely composed of heterogeneous entities, including HCLv with variable expression of CD11c (75%-87%) and CD103 (47%-75%) and other diseases with diverse morphologic features; many of those diseases have properties comparable to variants of SMZL and prolymphocytic leukemia.

In the current literature, HCLv is described to have a prolymphocyte-like single nucleolus in centrally located nuclei and villous cytoplasmic projections. However, hairy cells with a prominent nucleolus were well documented in the initial landmark work on HCL in 1958. HCLv-like cases without prominent nucleoli were also described in recent studies. The hairy or villous cytoplasm alone may have a wide spectrum of morphologic variations as summarized recently, including artifact, well discussed in the early studies of hairy cells.

The CD25– cases, HCLv and SMZL, also share histologic features. Instead of the nonaggregating interstitial infiltrate typical of HCL, lymphoid aggregates are common in all others, and an intrasinusoidal infiltrate in the spleen or marrow represented more than 20% of cases in the largest series of HCLv, 7 of 10 cases in a more recent report, all marrow biopsies of SRPL cases, and 43% of our cases. The occasional CD103+ prolymphocytic leukemia and DLBCL cases in our study and described in the literature have always lacked CD25 expression, further deviating from classical HCL.

There has been only a handful of clinical studies on HCLv reported in the literature; most articles are case reports. The CD25–, CD103+ B-lymphoproliferative disorder in our study constituted approximately 0.5% of all adult leukemia or 0.2% of lymphoproliferative disorders. The rarity of these cases makes any clinical studies with significant statistical power exceedingly difficult. When compared with HCL, the patients tend to be older and typically have moderate leukocytosis and peripheral lymphocytosis without monocytopenia. These features are reminiscent of HCLv and SMZL. Despite the fact that only a small number of our CD25– cases had relevant follow-up data, our findings still represent a significant addition to the current literature (Table 4).

Collectively, a low response rate to standard treatment for HCL has been observed in all published reports on HCLv, with CR rates consistently no better than 25%. In addition, there was essentially no response to interferon-alfa. For the benefit of clinical management, classical HCL ought to be clearly separated from other CD103+ B-lymphoproliferative disorders that lack CD25 expression, such as HCLv, SRPL, and SMZL, as well as prolymphocytic leukemia. Despite their variable expression of CD103 and variable hairy cytoplasm, most of these cases may be better considered “villous (hairy) cell variants” of marginal zone lymphoma rather than a variant of true HCL, especially because the nondiscriminative use of...
terms between HCL and HCLv may confuse proper therapy in clinical settings. In the 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues, HCLv and SRPL have been listed under an umbrella term “splenic B-cell lymphoma, unclassifiable”; HCLv is no longer considered to be biologically related to HCL. Although patients may be empirically treated with cladribine and pentostatin, it should be recognized that they typically require additional therapies. Treatment with rituximab, and alemtuzumab (Campath-1H) may be useful options owing to the strong expression of CD20, CD22, and CD52. Our data also emphasize that expression of CD25 ought to be evaluated in the routine workup of HCL, especially when analysis of annexin-A1 expression is not feasible.

We analyzed the largest series of CD103+ B-lymphoproliferative disorders in the literature. While cases coexpressing CD25 and annexin-A1 are characteristic of HCL, cases lacking CD25 and annexin-A1 seem to deviate from HCL and more closely relate to variants of SMZL. Although a precise diagnosis depends on a multimodal approach, separating the 2 groups should provide useful guidance in improving patient care.

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References


