Primary Lymph Node Plasmacytomas (Plasmacytic Lymphomas)

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A b s t r a c t

To determine whether primary lymph node plasmacytoma (PLNP) is a distinct entity among other types of plasma cell neoplasia, we analyzed a large series of PLNPs from 2 large lymphoma registries to compare histologic, immunophenotypic, and clinical features of PLNPs, nonnodal extramedullary plasmacytomas, and multiple myeloma. Twenty-five PLNPs (clinical data on 15 cases) were compared with 10 non–lymph node plasmacytomas and 51 cases of multiple myeloma; 36 cases of reactive plasmacytoses were used as controls. The histologic features of PLNP and other extramedullary plasmacytomas were similar. The histologic features of PLNPs were more immature than those of reactive plasmacytoses and less immature than in multiple myeloma. The immunophenotype of PLNPs significantly differed from that of reactive plasmacytoses, other extramedullary plasmacytomas, and multiple myeloma. PLNPs did not progress to multiple myeloma, unlike other extramedullary plasmacytomas, even though survival in PLNPs and other extramedullary plasmacytomas was similar. Our findings suggest that PLNPs may be distinct from other plasma cell dyscrasias.

Primary lymph node plasmacytomas (PLNPs) are rare malignant neoplasms.1-20 PLNPs represent 2% of all extramedullary plasmacytomas,19 0.5% of lymph node malignant neoplasms,8 and only 0.08% of all plasma cell malignant neoplasms.20 PLNPs can be diagnosed only after exclusion of metastatic multiple myeloma (which metastasizes to lymph nodes in up to 40% of cases of advanced-stage disease)19 and metastatic upper respiratory tract plasmacytomas (which represent 76% of extramedullary plasmacytomas and infiltrate cervical lymph nodes in approximately 15% of cases).19 A total of 33 PLNPs have been described, primarily as single case reports, 7 of them arising in Castleman disease (CD), plasma cell type.9,21-26

The 26 PLNPs not associated with CD1-7,10-20 showed a male preponderance (16 of 26 cases). The average age of the 26 patients was 56 years (range, 10-72 years). The tumors usually manifested as a localized mass (22 of 26 cases) in the neck (18 of 20 cases). Except for neck swelling, most PLNPs were asymptomatic. The lymph nodes excised were large (average size, 4.6 cm; range, 2-10 cm) and frequently were associated with serum monoclonal proteins (6/14 cases [43%]). The serum monoclonal proteins and plasma cell immunoglobulin expression were usually of IgG kappa type (3 of 6 reported cases of paraproteinemia). Focal amyloid deposition has been reported in 2 of 5 cases. Most patients had localized disease at initial diagnosis and were cured (15 of 21 cases) after local excision or radiation therapy. Patients with disseminated disease frequently died of disease (2 of 4 cases), which spread by lymph node rather than osseous metastasis. Only 1 described patient with disseminated disease has been cured with myeloma-type chemotherapy (melphalan and prednisone).10
PLNP reported in association with CD manifests with systemic lymphadenopathy typical of plasma cell CD (cervical, 2; axillary, 2; mediastinal, 1; and inguinal, 1).\textsuperscript{21-26} PLNP in CD occasionally metastasizes to bone, forming solitary sclerotic bone lesions (typically has demonstrated lambda-restricted monoclonal proteins or plasma cell immunoglobulin expression). PLNP with CD may be associated with a POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes; 2 of 6 cases).\textsuperscript{27} The size of lymph nodes (average, 5.8 cm; range, 3.5-10 cm), age of patients (average, 50 years; range, 38-56 years), male predominance (4 men, 2 women), frequency of amyloid deposition (1 of 3 cases), and frequency of serum monoclonal protein (3 of 5 cases) in PLNPs with CD are similar to PLNPs not associated with CD. Patients with PLNP and CD (especially those with POEMS syndrome) have disease that is often refractory to treatment with corticosteroids, chemotherapy, or radiation.

In the Kiel classification,\textsuperscript{28} primary lymph node plasmacytomas were designated as plasmacytic lymphomas. The Revised European-American Classification of Lymphoid Neoplasms (also called the REAL classification),\textsuperscript{29} however, lists extramedullary plasmacytomas and multiple myeloma as a single-spectrum disease with similar histologic, immunophenotypic, and clinical behavior. We investigated whether PLNP may be a distinct type of plasma cell neoplasia. We collected a large series of PLNPs from 2 large lymphoma registries to compare histologic, immunophenotypic, and clinical features of PLNP with other plasma cell neoplasms and reactive plasmacytosis.

Materials and Methods

We identified cases of PLNP from 2 large lymphoma registries (aggregate of about 200,000 lymphomas) through the computer archives. Disseminated multiple myeloma and extramedullary plasmacytoma were excluded by clinical examination for adjacent mucosal tumors, radiographic evidence of regional tumors, skeletal surveys, and bone marrow biopsy. Lymphoplasmacytic lymphomas with extensive plasmacytic differentiation\textsuperscript{30} were excluded by histologic identification of tumefactive masses of plasma cells without intervening small B lymphocytes typical of lymphoplasmacytic lymphomas. According to Greipp et al,\textsuperscript{31} plasma cell morphologic features were described as mature, immature, or plasmablastic. Mature plasma cells had dense clock-faced nuclear heterochromatin with abundant eccentric cytoplasm and inconspicuous nucleoli. Immature plasma cells showed more open, vesicular nuclear chromatin and prominent single nucleoli. Plasmablasts were distinguished by open vesicular nuclear chromatin with a prominent single nucleus and scant eccentric cytoplasm. Plasmablastic morphologic features were established by the histologic recognition of more well-differentiated plasma cell areas. Immunohistologic staining was performed according to the method of Hsu et al.\textsuperscript{32}

A broad panel of antibodies against a wide variety of hematopoietic antigens TABLE I was used that defined heavy-chain and light-chain restriction via cytoplasmic immunoglobulin staining, B-cell antigen expression, and expression of other hematopoietic antigens previously described in plasmacytomas or multiple myeloma.\textsuperscript{33,34} PLNPs that failed to show restricted immunoglobulin light-chain expression had paraffin blocks analyzed for immunoglobulin heavy-chain receptor gene rearrangements. DNA for gene rearrangement analysis was extracted from three 10-µm sections. The DNA was amplified with polymerase chain reaction, mineral oil was removed, and samples were extracted with chloroform. Ten microliters of each sample was run on a 3% agarose gel for 2 hours at 75 V. Fractions were stained with ethidium bromide and photographed. To detect a monoclonal JH rearrangement, the seminested primer system\textsuperscript{35} was used (primers Fr3A, LJH, and VLIH). Polymerase chain reaction was done with \textit{Taq} polymerase (GIBCO, Life Technologies, Rockville, MD) and performed in a thermocycler (Stratagene, LaJolla, CA). All primers were synthesized on a DNA synthesizer (Applied Biosystems, Foster City, CA).

The histologic, immunophenotypic, and clinical features of PLNPs were compared with those of an age- and sex-matched group of 10 non-lymph node extramedullary plasmacytomas, 51 previously published cases of multiple myeloma, and a control group of 36 reactive plasmacytoses. Extramedullary plasmacytomas were clonal as defined by restricted immunoglobulin light-chain expression or immunoglobulin gene rearrangement. Multiple myeloma cases were determined by the histologic identification of primary plasma cell neoplasms of bone accompanied by multiple lytic bone lesions and monoclonal serum or urine proteins. Reactive plasmacytoses were composed of dense aggregates of polyclonal plasma cells. Comparisons between groups for histologic and immunohistologic data were made with nonparametric methods for small sample sizes (Fisher exact test), and survival comparisons were made with the log-rank test and Kaplan-Meier survival curves.

Results

Primary Lymph Node Plasmacytomas

Review of the tissue registry at the first author’s institution yielded 172 cases of extramedullary plasmacytomas. Of
27 extramedullary lymph node plasmacytomas, 7 were excluded by clinical, radiographic, and bone marrow examinations as metastatic multiple myeloma (3) or extramedullary plasmacytomas (4), and 20 were primary lymph node neoplasms. After morphologic review of these 20 cases, 5 cases were excluded as lymphoplasmacytic (2) or immunoblastic (3) lymphomas. Review of 150,000 cases of lymphoma at another lymph node registry yielded 15 cases of plasmacytic lymphoma, 10 of which were confirmed by clinical and histologic review.

Of the total 25 PLNPs, the morphologic findings were mature in 15, immature in 5, and plasmablastic in 5 (Image 1). In most cases, the lymph node architecture was effaced by a diffuse proliferation of plasma cells Image 2. Occasionally, residual lymphoid follicles were identified, and only 1 case demonstrated lambda-restricted plasma cells with regressive transformation of follicle centers with a broad mantle zone lymphocytic proliferation characteristic of a localized type of plasma cell CD. Multinucleated plasma cells were more prominent in immature or plasmablastic tumors (Image 1B and Image 1C). Of 20 PLNPs stained with Congo red and immunohistologic stains, only 1 showed focal amyloid deposition. Seventeen PLNPs (85%) showed immunoglobulin light-chain restriction (kappa, 13; lambda, 4). Sixteen cases showed restricted immunoglobulin heavy-chain staining; gamma in 10, mu in 4, and alpha in 2. The 3 cases that did not demonstrate immunoglobulin light-chain restriction showed immunoglobulin heavy-chain gene rearrangement by molecular analysis of paraffin blocks. IgG kappa was the most common cytoplasmic immunoglobulin identified. The 1 case of CD showed IgG lambda cytoplasmic immunoglobulin expression. Most PLNP cases (15) showed gamma- or mu-restricted (not alpha-restricted) immunoglobulin heavy-chain staining. Two of the 3 PLNPs

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that did not show immunoglobulin light-chain restriction showed restricted immunoglobulin heavy-chain staining (IgG or IgM).

The ages of patients with PLNP ranged from 31 to 82 years (average, 60 years) at diagnosis. The male/female ratio was 16:9. Monoclonal proteins were detected in 12 (55%) of 22 patients who underwent serum immunoelectrophoresis and in 2 (13%) of 15 who underwent urine immunoelectrophoresis. Serum protein electrophoresis demonstrated monoclonal spikes in 3 (20%) of 15 PLNPs, ranging from 0.77 g/dL (7.7 g/L) to 3.3 g/dL (33 g/L). The 25 PLNPs manifested with cervical (14 [56%]), abdominal (4 [16%]), mediastinal (3 [12%]), axillary (2 [8%]), or inguinal (2 [8%]) lymphadenopathy. The lymph nodes ranged from 1 to 8 cm in size (average, 3.1 cm). Radiographic and endoscopic evaluation (15 PLNPs) showed that 13 patients had localized (stage I) disease, and 2 patients had disseminated lymphadenopathy on both sides of the diaphragm (stage III). Bone marrow examinations at diagnosis demonstrated no evidence of multiple myeloma. All patients with PLNP were without lytic bone lesions.

Treatment and follow-up (average, 5.9 years; range, 2 months to 21 years) for 12 of 15 patients with PLNP who were evaluated clinically showed that 10 had localized (stage I) disease and 2 had disseminated lymph node disease. Of the 10 patients with localized disease who had relapse had an isolated lytic bone lesion in the radius 1 year after resection and in a rib 6 years later and received additional radiation therapy (4,000 rad [40 Gy]) but were subsequently free of disease at 3 years and 15 years after diagnosis.

In 1 patient with localized PLNP in whom surgical and radiation therapy failed, disseminated (stage III) lymphadenopathy developed in association with severe systemic symptoms: the systemic dissemination was unresponsive to chemotherapy (melphalan 12 mg/d for 5 days for 2 courses and prednisone 15 mg/d), and the patient died 4 months after diagnosis. Of the 2 patients with disseminated PLNP at diagnosis, 1 was without evidence of disease 3 years after receiving chemotherapy (chlorambucil, 6 mg alternating with 4 mg every other day for 8 weeks), and 1 patient who received chemotherapy (chlorambucil, 4 mg alternating with 2 mg every other day and prednisone, 20 mg alternating with 10 mg every other day) died of disease 2 months after diagnosis. Disseminated osseous disease (myeloma) did not develop in any patient with PLNP. Approximately half of patients with PLNP survived for 10 years after diagnosis, and only 2 have died, both of disseminated lymph node disease, which was associated with immature (1) or plasmablastic (1) morphologic features at initial diagnosis.

Other Extramedullary Plasmacytomas

The non–lymph node–based extramedullary plasmacytomas were also mature (7 cases), immature (2 cases), and plasmablastic (1 case). No case showed amyloid deposition. Seven (70%) of the 10 cases showed immunoglobulin light-chain restriction (kappa, 5; lambda, 2). Six cases

### Table 1

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen-Cluster Designation</th>
<th>Main Reactivity</th>
<th>Source</th>
</tr>
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<tbody>
<tr>
<td>Anti-gamma</td>
<td>—</td>
<td>Ig heavy-chain gamma</td>
<td>DAKO, Carpinteria, CA</td>
</tr>
<tr>
<td>Anti-alpha</td>
<td>—</td>
<td>Ig heavy-chain alpha</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-mu</td>
<td>—</td>
<td>Ig heavy-chain mu</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-delta</td>
<td>—</td>
<td>Ig heavy-chain delta</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-epsilon</td>
<td>—</td>
<td>Ig heavy-chain epsilon</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-kappa</td>
<td>—</td>
<td>Ig light-chain kappa</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-lambda</td>
<td>—</td>
<td>Ig light-chain lambda</td>
<td>DAKO</td>
</tr>
<tr>
<td>L26</td>
<td>20</td>
<td>B cells</td>
<td>DAKO</td>
</tr>
<tr>
<td>MB2</td>
<td>—</td>
<td>B cells</td>
<td>Biotest, Dreieich, Germany</td>
</tr>
<tr>
<td>MT2</td>
<td>43</td>
<td>T cells</td>
<td>Biotest</td>
</tr>
<tr>
<td>DFT-1</td>
<td>14</td>
<td>T cells</td>
<td>DAKO</td>
</tr>
<tr>
<td>UCHL-1</td>
<td>CD45RO</td>
<td>T cells</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-Leu-7</td>
<td>57</td>
<td>NK cells</td>
<td>Becton Dickinson, Heidelberg, Germany</td>
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<tr>
<td>Ber-H2</td>
<td>30</td>
<td>B- and T-cell activation, Hodgkin cells</td>
<td>Behringwerke, Marburg, Germany</td>
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<tr>
<td>KP-1</td>
<td>68</td>
<td>Macrophages</td>
<td>DAKO</td>
</tr>
<tr>
<td>Leu-M1</td>
<td>15</td>
<td>Mature neutrophils, Hodgkin cells</td>
<td>DAKO</td>
</tr>
<tr>
<td>Anti-LCA</td>
<td>45</td>
<td>Leukocytes</td>
<td>DAKO</td>
</tr>
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Ig, immunoglobulin; LCA, leukocyte common antigen.
showed restricted immunoglobulin heavy-chain staining (gamma, 3; alpha, 2; mu, 1). The 3 cases that did not demonstrate immunoglobulin light-chain restriction showed immunoglobulin heavy-chain gene rearrangement by molecular analysis of paraffin blocks. The ages of the patients with non–lymph node plasmacytomas ranged from 57 to 80 years (average, 68.5 years) at diagnosis. The male/female ratio was 7:3. Serum protein electrophoresis demonstrated monoclonal spikes in 3 (33%) of 9 patients, ranging from 0.4 g/dL (4 g/L) to 3.7 g/dL (37 g/L). Of 8 patients who had urine immunoelectrophoresis, 3 (38%) showed a monoclonal protein. Sites of disease manifestation in the 10 cases were upper respiratory tract (5 [50%]), oral cavity (2 [20%]), lung (1 [10%]), stomach (1 [10%]), and kidney (1 [10%]). The sizes of the plasmacytomas ranged from 1 to 28 cm (average, 5 cm).

All patients had localized (stage I) disease at initial diagnosis. Bone marrow examinations at diagnosis were without evidence of myeloma. All patients were without lytic lesions. All patients had surgical excision, except for the patient with the lung plasmacytoma, who received radiation. After follow-up of 1.8 to 12.7 years (average, 6.3 years), 6 patients were without evidence of disease, 1 had persistent disease (lung plasmacytoma), 2 had recurrent tumors without lymph node metastasis, and 1 developed multiple myeloma and died of disease. None of the patients showed disseminated lymph node metastasis. Of the 2 patients with disease recurrence, the disease in 1 showed plasmablastic and in 1 immature plasma cell morphologic features. The patient in whom multiple myeloma developed showed immature plasma cells at diagnosis.

Multiple Myeloma

The 51 cases of multiple myeloma showed immature (41 cases) or plasmablastic (10 cases) plasma cells at diagnosis. The bone marrow plasma cells constituted 12.5% to 92.5% (average, 47%) of nucleated cells in the bone marrow. Of the 51 cases, 46 (90%) showed restricted immunoglobulin light-chain expression (kappa, 24; lambda, 22). Thirty cases showed restricted immunoglobulin heavy-chain staining (gamma, 21; alpha, 8; delta, 1). Of the 5 cases without restricted immunoglobulin light-chain expression, 3 showed restricted immunoglobulin heavy-chain expression and 2 had serum monoclonal proteins. Tissue was not available for immunoglobulin gene rearrangement analysis. The ages of the patients with multiple myeloma ranged from 18 to 79 years (average, 60 years). Patients had multiple skeletal lesions or diffuse osteopenia (2 cases) and serum or urine monoclonal proteins. They received melphalan- and prednisone-based chemotherapy. Twenty-three patients had follow-up, which ranged from less than 1 year to 9 years (average, 3 years), and 20 died of disease.

Reactive Plasmacytoses

The reactive plasmacytoses showed mature plasma cells in all 36 cases. In all cases, plasma cells expressed kappa and lambda immunoglobulin light chains and multiple immunoglobulin heavy chains (gamma and alpha, 30; gamma, alpha, and mu, 6). Patients with reactive plasmacytoses had diagnoses of inflammatory disorders in 25 cases, Hodgkin disease in 1, CD (plasma-cell type) in 4, and plasmacytoses associated with carcinoma in 6. The ages of the
patients ranged from 8 days to 80 years (average, 51 years) at diagnosis.

Discussion

Laboratory and Clinical Comparisons

Immunohistologic comparisons between PLNPs, other extramedullary plasmacytomas, multiple myeloma, and reactive plasmacytoses (the control group) demonstrated immunohistologic differences between PLNPs and reactive plasmacytoses \( P = .014 \) or less, other extramedullary plasmacytomas \( P = .008 \) or less), and multiple myeloma \( P < .023 \). \(^3\) PLNPs showed decreased leukocytic common antigen (LCA) expression \( P < .001 \) compared with reactive plasmacytosis \(^4\) Table 2. PLNP showed increased expression of CD30 \( P = .04 \) \(^5\) Image 3 compared with other extramedullary plasmacytomas. PLNPs showed decreased expression of the B-cell antigen MB2 \( P = .004 \) and decreased expression of the T-cell-related antigen CD45RO \( P = .032 \) compared with multiple myeloma. Phenotypic differences in the expression of other antigens listed in Table 1 were not significant. Survival of patients with PLNP was not significantly different from that of patients with other extramedullary plasmacytomas. Survival of patients with multiple myeloma was significantly worse than that of patients with PLNPs and other extramedullary plasmacytomas \( P < .001 \) \(^1\) Figure 1. Plasmablastic morphologic features were associated with poor survival in plasma cell neoplasms \( P < .001 \) \(^2\) Figure 2. Immature or plasmablastic morphologic features were associated with dissemination, death, and disease recurrence in PLNPs and the development of myeloma in patients with non–lymph node extramedullary plasmacytomas.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>RP (n = 36)</th>
<th>PLNP (n = 25)</th>
<th>EM NLP (n = 10)</th>
<th>MM (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphologic features</td>
<td>Mature, 36</td>
<td>Mature, 15; immature, 5; plasmablastic, 5</td>
<td>Mature, 7; immature, 2; plasmablastic, 1</td>
<td>Mature, 0; immature, 41; plasmablastic, 10</td>
</tr>
<tr>
<td>Phenotype (10% or more plasma cell staining)</td>
<td>Leukocyte common antigen</td>
<td>24</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>CD30</td>
<td>24</td>
<td>5*</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>MB2</td>
<td>14</td>
<td>1*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>CD45RO</td>
<td>1</td>
<td>0*</td>
<td>8*</td>
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<tr>
<td>Clinical development of MM</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of metastasis</td>
<td>None</td>
<td>Lymph node</td>
<td>Bone marrow</td>
<td>Bone marrow</td>
</tr>
</tbody>
</table>

EM NLP, extramedullary non–lymph node plasmacytoma; MM, multiple myeloma; PLNP, primary lymph node plasmacytoma; RP, reactive plasmacytosis.

\( n = 12 \).

\( n = 23 \).

Conclusions

Histologic and clinical analysis of PLNPs corroborated the findings of previous case reports that PLNPs are rare hematologic neoplasms that usually manifest with cervical lymph node enlargement, typically show effacement of lymph node architecture by mature plasma cells, and usually are cured with surgical excision or radiation therapy. Only rarely do PLNPs demonstrate focal amyloid deposition or regression of germinal centers and mantle zone proliferation diagnostic of plasma cell CD. PLNPs may manifest with disseminated lymphadenopathy that usually does not progress to multiple myeloma, in contrast with other types of extramedullary plasmacytomas. PLNPs with disseminated lymph node spread may be cured by chemotherapy (chlorambucil in our study or melphalan and prednisone as previously reported). The rare patients with disseminated PLNP who do not respond to chemotherapy often die of disease. The survival time of patients with PLNP, like that of patients with other types of extramedullary plasmacytomas, is significantly longer than the survival of patients with multiple myeloma.

PLNPs, other types of extramedullary plasmacytomas, and multiple myeloma have a similar cytomorphic spectrum of plasma cell differentiation, whereas reactive plasmacytoses are composed of only mature plasma cells. Thus, the finding of immature or plasmablastic plasma cell morphologic features was diagnostic of plasma cell neoplasia (PLNP, other extramedullary plasmacytomas, or multiple myeloma) and was most characteristic of multiple myeloma, which usually demonstrated immature plasma cell morphologic features. Because most PLNPs and other types of extramedullary plasmacytomas show mature plasma cell morphologic features relatively often and because reactive plasmacytoses form dense tumefactive plasma cell infiltrates simulating plasmacytoma in multiple body sites, as previously reported in the upper respiratory tract, \( ^{36} \) clonality assessment by immunohistologic staining or gene rearrangement analysis...
was essential for distinguishing plasmacytomas from reactive plasmacytoses.

Only a minority of PLNPs, other extramedullary plasmacytomas, and multiple myeloma show plasmablastic morphology (Table 2), which can make distinction from immunoblastic lymphoma or other poorly differentiated hematopoietic and nonhematopoietic neoplasms very difficult. Diligent morphologic analysis was essential in this context because review of multiple sections of plasmablastic plasma cell tumors usually shows areas of immature plasma cell morphologic features. Immunohistologic detection of leukocytic common antigen CD45, B-cell antigen CD20, T-cell–associated antigens (plasmablastic multiple myeloma only), CD30, and CD68 cannot be used to distinguish a B-cell, T-cell, anaplastic large cell, or true histiocytic lymphoma from plasmablastic plasma cell neoplasms because plasmablastic types of plasma cell tumors also may express these antigens.34 Histologic identification of immature plasma cell differentiation and immunoglobulin light- and heavy-chain expression were the best criteria for distinguishing plasmablastic plasma cell tumors from acute lymphoblastic and nonlymphoblastic leukemias or from poorly differentiated sarcomas and poorly differentiated carcinomas. According to our findings, metastatic malignant melanoma, although it may be histologically similar to plasmablastic plasma cell neoplasms, was not a problem in the differential diagnosis because plasmablastic plasma cell tumors were consistently HMB-45 negative (data not shown).

The differences in immunophenotype and systemic lymph node rather than osseous metastasis in PLNPs suggest that PLNPs may be distinct from other types of plasma cell neoplasia (Table 2). The differences in phenotype and biologic behavior may be related to a more benign genotype or different precursor cell compared with other plasmacytomas or multiple myeloma. Genotypic analysis of plasma cells in PLNPs will be needed to determine whether they show fewer genotypic abnormalities compared with other types of plasma cell neoplasia and lack somatic hypermutations characteristic of prefollicular B-cell precursors associated with paracortical T-cell nodules of lymph node paracortex.37,38 Plasma cells of multiple myeloma demonstrate somatic hypermutation of immunoglobulin light-chain variable regions characteristic of post–germinal center derivation39,40 and are accompanied by circulating preplasma cell precursors that can adhere to bone marrow stromal cells and differentiate to plasma cells after in vitro exposure to the cytokine interleukin-6.41 Analysis of peripheral blood samples from patients with PLNPs and other extramedullary plasmacytomas is needed to determine whether they may be less frequently associated with circulating preplasma cell precursors, which may explain the differences in clinical patterns of dissemination of PLNP compared with other extramedullary plasmacytomas and multiple myeloma.

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