Marginal Zone Lymphomas With Plasmacytic Differentiation and Related Disorders

Thierry J. Molina, MD, PhD,1 Pei Lin, MD,2 Steven H. Swerdlow, MD,3 and James R. Cook, MD, PhD4

Key Words: Society for Hematopathology/European Association for Haematopathology Workshop; Marginal zone lymphomas; Plasmacytic differentiation

DOI: 10.1309/AJCP63OGXHXCSKSC

Abstract

Marginal zone lymphomas of all types (nodal, splenic, and extranodal mucosa-associated lymphoid tissue [MALT]) may show plasmacytic differentiation. Distinguishing marginal zone lymphomas from other small B-cell lymphomas with plasmacytic differentiation, especially lymphoplasmacytic lymphoma, or from plasma cell neoplasms may be challenging. Marginal zone lymphomas with plasmacytic differentiation were discussed in 2 sessions of the 2009 Society for Hematopathology/European Association for Haematopathology Workshop. Session 4 focused on nodal marginal zone lymphomas, including cases exhibiting classic features and cases displaying atypical phenotypes. The difficulties of classification of cases with increased numbers of large cells were also discussed. Session 5 examined nonnodal marginal zone lymphomas and related entities, including splenic marginal zone lymphoma, MALT lymphoma, γ heavy chain disease, and cryoglobulin-associated lymphoproliferative disorders. These cases illustrate the importance of clinical data and, in some cases, phenotypic and cytogenetic findings in appropriately applying the 2008 World Health Organization criteria.

The marginal zone lymphomas (MZLs) are a heterogeneous group of neoplasms that resemble the normal B-cell populations of the marginal zone. The 3 recognized subtypes (nodal, splenic, and extranodal) each show partially overlapping features, and each may frequently show plasmacytic differentiation.1 The differential diagnosis in these cases often may include lymphoplasmacytic lymphoma (LPL) or other low-grade B-cell lymphoproliferative disorders with plasmacytic differentiation. Two sessions of the 2009 Society for Hematopathology/European Association for Haematopathology Workshop were devoted to discussion of MZLs and related entities: one (session 4) focused on nodal MZL (NMZL), and another (session 5) included discussions of splenic MZL (SMZL), extranodal mucosa-associated lymphoid tissue (MALT) lymphoma, γ heavy chain disease (γ-HCD), and mixed cryoglobulinemia (MC).

Nodal MZL

NMZL is a primary nodal B-cell neoplasm that resembles extranodal or SMZL involving lymph nodes, without evidence of extranodal or splenic disease.2 Cytologically, NMZL may show varying proportions of small lymphocytes, marginal zone–like cells, centrocyte-like cells, monocytoïd B cells, and scattered transformed B cells.3,4 Plasma cell differentiation is a well-described feature of MZL that was reported in 2 (33%) of 6 cases of a series of NMZL of “splenic type,”5 and 22% to 38% in other series of NMZL.6-8

NMZL is a rare entity (1%-2% of all lymphoid neoplasms) that lacks characteristic phenotypic or molecular patterns,
In the Non-Hodgkin Lymphoma Classification Project’s study of the reproducibility of the diagnosis of NMZL,9 there was 53% consensus between expert pathologists based on histologic features, 63% based on histologic features and immunohistochemical results, and 63% with the addition of clinical information. The median age is about 60 years,10 and patients have asymptomatic, localized disease or disseminated disease, mainly with peripheral and abdominal lymphadenopathy. There may be blood and bone marrow involvement, and the bone marrow growth pattern is similar to that in other MZLs. There is no involvement of an extranodal MALT site or spleen. Hepatitis C virus (HCV) infection has been reported to range from 0% to 20%, and light chain/heavy chain deposition disease has been described once.11

The phenotype is usually CD5−/CD23−/CD10−/BCL6−/BCR. There is predominant V
t
3 and V
3 usage, and trisomy 3, 18, and 17 have been described, but these findings are not specific for NMZL. The translocations associated with extranodal MALT lymphomas are not present. Tumor cells are considered to be derived from post–germinal center marginal zone B cells and show predominantly mutated BCR, distinct from rodent marginal zone B cells that bear mostly unmutated BCR.12

In the NMZL session, 24 cases were reviewed. One of the critical points discussed was related to the criteria used to diagnose NMZL In 5 cases, the panel was only able to diagnose small B-cell lymphoma with plasma cell differentiation owing to absence of enough clinical information or owing to submission of posttherapeutic cases without knowledge of the pretherapeutic diagnostic samples. Bone marrow localization alone in the absence of full clinical information did not allow the panel to distinguish between the various small B-cell lymphomas, and such cases were descriptively classified as CD5− small B-cell lymphomas with plasmacytic differentiation.

A marginal zone growth pattern, germinal center remnants, follicular colonization, and/or disruption of follicular dendritic cell (FDC) meshworks in immunohistochemical studies are helpful features to suggest a diagnosis of NMZL, but these findings may not be present in all cases.13 Case 319 demonstrated most of the characteristic features of an MZL involving a lymph node. In this case, a 67-year-old woman had cervical lymphadenopathy for 8 years with a monotypic IgM spike. Cervical lymph node biopsy showed typical nodular architecture with a pale, peripheral, monocytoid area and a dark central centrocytoid area; and plasmacytic differentiation at the periphery. Some remnants of BCL6+ germinal center cells were present. Scattered large cells were present in the monocytoid areas, particularly at the periphery of the colonized follicles as shown by Ki-67 staining. Although the panel fully agreed that this case was prototypical of an MZL involving lymph node with plasmacytic differentiation, it was not classified as a definitive NMZL because in the absence of clinical information regarding the distribution of disease or history of therapy received, the possibility of secondary nodal involvement by a SMZL or extranodal MALT lymphoma could not be completely excluded.

As discussed in detail in the article by Lin et al in this issue of the Journal,14 one of the most difficult differential diagnoses in the evaluation of a nodal small B-cell lymphoma with plasmacytic differentiation is NMZL vs LPL. Case 187 was a lymph node containing a CD5− small B-cell lymphoma with marked plasmacytic differentiation. However, in this case, the marked plasmacytic differentiation occurred without FDC staining associated with the tumor in most parts of the lymph node, and FDC meshworks were present only in the residual cortical areas. Therefore, the panel favored LPL over MZL.

Some other cases were difficult to differentiate between LPL involving lymph node and MZL with plasma cell differentiation, especially when there was mainly plasma cell differentiation in a perifollicular pattern without an obvious neoplastic B-lymphoid-cell population. In this context, the presence of perifollicular IgD+ lymphoid cells, in addition to a perifollicular monotypic plasma cell population, may help, but it can be difficult to differentiate IgD+ neoplastic marginal zone cells from benign mantle cells. Therefore, flow cytometric data may be helpful to demonstrate the monotypic profile of the IgD+ subpopulation (case 320).

When MZL involves a lymph node, full clinical data and history are essential to exclude extranodal MZL or SMZL involving lymph nodes. Fluorescence in situ hybridization (FISH) looking for MALT-associated translocations can help, but a history of autoimmune disease such as Sjögren syndrome makes it difficult to differentiate between NMZL and extranodal MZL involving lymph node. Therefore, the panel suggests classifying such cases as a MZL involving lymph node (case 256) and providing a differential diagnosis of NMZL vs secondary nodal involvement by SMZL or MALT lymphoma.

Criteria for large cell transformation in NMZL are not well defined, and cases with apparently increased numbers of large cells may be challenging. It is sometimes difficult to differentiate intermediate-sized marginal zone cells with a monocytoid appearance from large transformed cells. Giemsa stains may help to better demonstrate the nuclear features, but one should diagnose transformation to diffuse large B-cell lymphoma (DLBCL) only if sheets of large cells are seen. The importance of reserving a diagnosis of
DLBCL for cases with sheets of large cells is reinforced by the demonstration that there is no difference in progression-free survival in MZL with more than 20% scattered large cells vs cases with fewer than 20% large cells.\(^6\) Ki-67 stains alone should also not be used to diagnose transformation to DLBCL because there is no agreed-on cutoff for making this distinction. Clinical data, including lactate dehydrogenase levels may help, but we cannot rely on such findings alone to establish a diagnosis of transformed DLBCL.

A related but distinct issue raised in this slide session concerned how we could recognize a low-grade NMZL component in the background of a DLBCL (cases 288, 307, and 369; Images 3C, 3D, and 3E). The cytologic features and phenotype of the small cell component and, when present, the FDC pattern or plasmacytic differentiation should be consistent with such a diagnosis.

When evaluating the numbers of large cells that may be present in a case of NMZL, it may often be difficult to distinguish between scattered, large, neoplastic B cells and residual, benign, partially colonized germinal centers. Immunohistochemical stains for CD10 and BCL6 may be helpful in recognizing colonized germinal centers. However, it has also been reported that the scattered large cells in MZL may also express BCL6.\(^6\) We, therefore, need additional studies of the regulation of BCL6 in marginal zone cells undergoing transformation to DLBCL and additional information regarding the prognostic significance of increased but scattered numbers of large cells.

**Image 1** (Case 319) Marginal zone lymphoma localization in lymph node. A and B, Nodular architecture with biphasic pattern with central dark area and paler peripheral area (H&E, low power). C, Pale monocytoid area with scattered B-blast (left) and plasma cell differentiation in the internodular area (right) (H&E). D, Dark centrocytoid area.
Image 2 (cont) **E**, Plasma cell differentiation area with numerous Dutcher bodies (H&E). **F**, Few remnants of germinal center cells are present in the center of some colonized follicles (BCL6). **G**, Numerous Ki-67+ cells in the remnant of germinal centers; scattered Ki-67+ cells mainly localized at the internal part of the monocytoid area.

**Image 2** (Case 187) Lymphoplasmacytic lymphoma favored over nodal marginal zone lymphoma. **A**, The follicular dendritic meshwork is present only in the remnant of the cortex, whereas most of the lymphoma with plasmacytic differentiation is not associated with follicular dendritic cells (CD21, low power). **B**, Remnant of the cortical follicular dendritic cell network partly destroyed by the lymphoma (CD21, high power).
CD5+ NMZL with plasma cell differentiation was favored in 4 cases over B-cell chronic lymphocytic leukemia (B-CLL) with plasma cell differentiation (cases 102, 137, 160, and 211). The presence of monocytoid areas or a perifollicular pattern were findings favoring a diagnosis of NMZL. Image 4A, Image 4B, Image 4C, Image 4D, Image 4E, Image 4F, Image 4G, and Image 4H. However, differentiation of monocytoid areas with scattered blasts from proliferation centers is sometimes difficult. Image 4I. Flow cytometric or cytogenetic studies may assist in some cases by showing a typical B-CLL phenotype or chromosomal abnormalities encountered in B-CLL. However, there seem to be cases with intermediate features or morphologic variation between initial diagnosis and relapse. Additional studies of interfollicular or perifollicular B-CLL/small lymphocytic lymphoma and CD5+ NMZL are needed to further clarify the CD5+ subtype of NMZL.

Finally, Case 43 involved a 26-year-old woman with an 18-year history of adenopathy. The biopsy showed a perifollicular monotypic plasma cell expansion surrounded by “monocytoid-like” lymphoid cells. However, the monocytoid-like cells were, in fact, CD3+ T cells that expressed CD57, and polymerase chain reaction (PCR) did not show clonality despite the monotypic plasma cells. This case was suggestive

Image 3A Increased large cells in nodal marginal zone lymphoma (NMZL). A, Marginal zone area with middle-sized cells and rare large B cells (Giemsa). B, Marginal area with increased large B cells, but they are not cohesive; no criteria for transformation in diffuse large B-cell lymphoma; large cells (arrows) have open chromatin and larger nucleoli than the middle-sized cells (Giemsa). C-E (Case 288) Large B-cell lymphoma arising from a probable marginal zone lymphoma. C, Large B cells are admixed with middle-sized cells having plasma cell differentiation and mitosis (Ki-67). D, Ki-67+ cells between 85% and 100% of cells.
of an immunoregulatory disorder, perhaps analogous to autoimmune lymphoproliferative syndrome, although evaluation for this syndrome was negative.

Overall, this session exemplified how difficult it is to definitively diagnose NMZL without full clinical history, especially when plasmacytic differentiation is present. Fine cytologic analysis, FDC staining by immunohistochemical stains, and knowledge of the existence of phenotypic variation (BCL6 expression in large cells, CD5 in some cases) are crucial to recognize NMZL. Flow cytometric analysis and cytogenetic data (mostly owing to absence of classical recurrent abnormalities encountered in the other subtypes of lymphoma) are also very helpful in some cases. Finally, the difficulties in using Ki-67 stains to diagnose transformation to large cell lymphoma is often linked to the presence of numerous germinal center remnants with a high percentage of positive cells that are reactive admixed with tumor cells colonizing these follicles.

Extranodal MZL

Extranodal MZLs of the MALT type (MALT lymphomas) are lymphomas that recapitulate the features seen in benign, acquired MALT tissue.15,16 Prototypical examples, such as those arising in the stomach, display all of the histologic findings seen in acquired MALT, including reactive germinal centers, an expanded interfollicular marginal zone B-cell proliferation, and B cells that infiltrate overlying epithelium.17,18 It is important to realize, however, that the specific histologic findings in any given case may vary dramatically between anatomic sites.19-21 For example, lymphoepithelial lesions are found in the great majority of cases arising in the stomach, but they are rare in cutaneous MZLs. Similarly, overt monocytoid morphologic features are found in nearly all cases of MALT lymphoma arising in the parotid gland, but such cytologic features are uncommon in ocular adnexa MALT lymphomas.21 The spectrum of morphologic features found in extranodal MALT lymphoma
Image SI (Case 211) CD5 + nodal marginal zone lymphoma.

A-E, Numerous remnants of partially colonized germinal centers [A], with centrocytoid [B], monocytoid [C and D], and plasmacytic areas [E] (A-E, Giemsa).
Molina et al / MZL With Plasmacytic Differentiation

Table 1
Cases of Extranodal Mucosa-Associated Lymphoid Tissue Lymphomas by Anatomic Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Case No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>166, 281</td>
</tr>
<tr>
<td>Large intestine</td>
<td>52, 374</td>
</tr>
<tr>
<td>Orbit</td>
<td>53, 177</td>
</tr>
<tr>
<td>Appendix</td>
<td>25</td>
</tr>
<tr>
<td>Uvea</td>
<td>29</td>
</tr>
<tr>
<td>Thymus</td>
<td>57</td>
</tr>
<tr>
<td>Thyroid</td>
<td>147</td>
</tr>
<tr>
<td>Skin</td>
<td>184</td>
</tr>
<tr>
<td>Tonsil</td>
<td>361</td>
</tr>
<tr>
<td>Kidney</td>
<td>362</td>
</tr>
<tr>
<td>Multiple sites</td>
<td>362</td>
</tr>
</tbody>
</table>

* Submitted to the 2009 Society for Hematopathology/European Association for Haematopathology Workshop.

Plasmacytic differentiation is found in approximately one third of cases of MALT lymphoma. Most commonly, plasmacytic differentiation takes the form of light chain–restricted plasma cells located in the interfollicular and perifollicular regions and/or within colonized germinal centers (Image 5A). In some cases, plasmacytoma-like morphologic features, with more than 80% of the total cellularity consisting of clonal plasma cells. Plasmacytoma-like features were illustrated in 2 workshop cases, cases 52 and 177, each of which displayed sheets of clonal plasma cells throughout the mass lesion (Image 5B). In these cases,
identification of a B-cell component of the neoplasm is essential to distinguish it from a pure plasma cell neoplasm. This may be accomplished through flow cytometric studies demonstrating a B-cell population with clonal surface immunoglobulin light chain restriction or through immunohistochemical studies demonstrating B cell–rich areas, lymphoepithelial lesions, or colonized germinal centers.

In some cases, it may be difficult to determine whether a B-cell proliferation and an accompanying clonal plasma cell proliferation are clonally related. Case 25 illustrated this difficult problem. In this case, an appendiceal mass was shown to be secondary to involvement by mantle cell lymphoma, which also involved the bone marrow. However, the appendiceal lesion also contained numerous κ light chain–restricted, cyclin D1– plasma cells. A clonal plasma cell proliferation was not present in the bone marrow. The consensus of the review panel was that this lesion represented a collision tumor composed of mantle cell lymphoma plus an unrelated plasma cell proliferation that likely represented a MALT lymphoma with plasmacytic differentiation. Paraffin section interphase FISH studies were positive for t(11;14) (q13;q32) in the lymphocytes, but not the plasma cells, confirming that these represent 2 clonally unrelated processes.

Because the majority of MALT lymphomas express IgM heavy chains, MALT lymphomas may be associated with IgM paraproteins, especially when overt plasmacytic differentiation is present. The finding of a B-cell lymphoproliferative disorder lacking CD5 and CD10 associated with an IgM paraprotein may raise the possibility of an LPL.

This sometimes challenging differential diagnosis was illustrated in case 281. In this case, transbronchial biopsy of a lung mass demonstrated an infiltrate of small B cells with focal monocytoid features. Only rare plasma cells were present, and these cells appeared polytypic by immunohistochemical studies. However, serum electrophoresis disclosed a 4.4-g/dL IgM κ monoclonal paraprotein, bone marrow biopsy showed 8% to 10% κ monoclonal plasma cells, and bone marrow flow cytometry showed a small (1%) κ monotypic B-cell population. This constellation of findings suggested a pulmonary MALT lymphoma with plasmacytic differentiation seen in the bone marrow but not in the sampled lung lesion vs a pulmonary MALT lymphoma and a coexisting, unrelated bone marrow–based plasma cell neoplasm vs LPL involving bone marrow and lung. FISH studies performed on the lung mass were positive for an API2/MALT1 translocation, a finding reported only in extranodal MALT lymphoma and in a minority of DLBCLs. This result confirmed that the pulmonary lesion represented an extranodal MALT lymphoma.

However, the relationship between the pulmonary lymphoma and clonal bone marrow plasma cell proliferation in the case remains uncertain. FISH studies for MALT lymphoma–associated abnormalities, including API2/MALT1, IGH/MALT1, or IGH/BCL10, may be helpful in routine practice. In the setting of a small B-cell lymphoproliferative disorder, the finding of one of these translocations essentially confirms a diagnosis of MALT lymphoma. However, the
incidence of these translocations varies dramatically with anatomic site, and none of these abnormalities is found in an overall majority of MALT lymphomas.24-26

Definitive evaluation of the relationship between the plasma cell and lymphocyte components in some cases may require isolating and sequencing the immunoglobulin heavy or light chains from the extramedullary and bone marrow lesions. Demonstration of an identical immunoglobulin rearrangement would provide very strong evidence of a clonal relationship between the 2 processes. Unfortunately, detailed sequencing studies are typically not possible in routine clinical practice. In such cases, an appropriate differential diagnosis should be provided to clinicians. When it is unclear whether bone marrow–based clonal plasma cell proliferations may represent lymphoma vs a plasma cell neoplasm, bone scans and quantitative immunoglobulin levels should also be suggested. The finding of lytic bone lesions or decreased normal immunoglobulin levels suggests the diagnosis of plasma cell myeloma. As discussed in the article by Lin et al in this issue of the Journal,14 such cases require close correlation with the clinical findings.

Splenic MZL

SMZL is a splenic-based B-cell neoplasm that resembles the B cells found in normal splenic marginal zones. These cells have generally been thought to represent post–germinal center “memory” B cells, but more recent data have suggested that at least a subset of normal marginal zone cells may represent a distinct B-cell subset that is independent of the germinal center reaction.12,27-29 Histologically, spleens involved by SMZL display a marked expansion of white pulp nodules, usually with accompanying infiltration of neoplastic B cells into the red pulp as well.27,30,31 In most cases, the white pulp nodules display a classic “biphasic” appearance, with central cores of small lymphocytes that resemble normal mantle zone cells surrounded by a rim of slightly larger lymphocytes with slightly irregular nuclear contours and moderate to abundant pale cytoplasm. There may be central residual germinal centers in some cases. The central core of small lymphocytes and the outer zone of monocytoid–appearing cells have been shown to be part of the neoplastic clone.28 In some cases, the white pulp nodules consist predominantly or exclusively of cells with monocytoid features. Phenotypically, SMZL is generally negative for CD5, CD10, CD23, and CD123. Most cases coexpress IgM and IgD, CD11c is frequently coexpressed, and there is surface immunoglobulin light chain restriction. The most frequent recurrent cytogenetic abnormality in SMZL is a del(7q),33,34 although this is found in only 25% to 40% of cases. As with other MZLs, trisomy 3 is seen in a subset of cases (approximately 20%-30%).32,35,36

Plasmacytic differentiation has been reported in 21% to 74% of cases.31,32,37,38 Most frequently, plasmacytic differentiation takes the form of monotypic plasma cells within the marginal zones or interfollicular areas or, in some cases, clustered within colonized germinal centers. Approximately one third of patients are reported to have a monoclonal paraprotein, usually of the IgM type. The presence of an IgM paraprotein may lead to concern for LPL. However, the levels of IgM in SMZL usually remain low, and serum hyperviscosity is unusual. Plasma cell proliferations in the bone marrow of patients with SMZL may also cause diagnostic confusion. For example, case 149 was an SMZL that showed no evidence of plasmacytic differentiation in the splenectomy specimen, but the bone marrow showed involvement by SMZL plus a clonal plasma cell proliferation with the same light chain. PCR studies performed on the spleen identified 1 clonal \( \text{IGH} \) rearrangement, whereas PCR performed on the bone marrow identified 2 bands, one of which matched that seen in the spleen. This case illustrates the use of PCR studies, which are available to most laboratories or through reference laboratories in routine practice, to suggest that the bone marrow–based plasma cell proliferation was likely a second clone, unrelated to the SMZL. However, a definitive assessment of the relationship between the SMZL and bone marrow plasma cells would require sorting of plasma cells and sequencing of the immunoglobulin rearrangements.

In the bone marrow, SMZL typically shows a nodular or interstitial growth pattern. Intravascular infiltration by
neoplastic B cells is also a characteristic feature, although this finding may also be seen in other B-cell lymphomas, and the presence of an intrasinusoidal growth pattern in the bone marrow is not sufficient for a definitive diagnosis of SMZL. A particularly difficult differential diagnosis is with splenic diffuse red pulp small B-cell lymphoma (SDRPSBCL), as illustrated by case 75.39,41 This uncommon, recently described neoplasm is considered a provisional entity in the 2008 World Health Organization classification. SDRPSBCL shows a morphologic bone marrow growth pattern and an immunophenotype that is identical to that seen in SMZL. Deletions of chromosome 7q also occur in both entities, and the cytologic features in the peripheral blood also overlap. The distinction between SDRPSBCL and SMZL is made entirely on the basis of splenic histologic features. In contrast with the typical white pulp expansion seen in SMZL, SDRPSBCL shows a diffuse replacement of the red pulp with little if any residual white pulp. This case illustrates that a completely definitive diagnosis of SMZL cannot be made on the basis of bone marrow and peripheral blood findings alone, but requires review of a splenectomy specimen. At present, it is unclear whether SMZL and SDRPSBCL should be treated differently, and so making this distinction may not be necessary for treatment in routine practice. Two of the cases submitted to the workshop (cases 132 and 297) were bone marrow biopsy specimens with features typical of SMZL. In the absence of a splenectomy specimen, the review panel favored a diagnosis of SMZL but believed a definitive diagnosis could not be established.

The 2008 World Health Organization classification also introduced a new category of “splenic B-cell lymphoma/leukemia, unclassifiable.”41 This new category was adopted to emphasize that many splenic-based lymphoproliferative disorders do not meet current diagnostic criteria for any well-established entity and to discourage the practice of simply classifying any small B-cell neoplasm with a nonspecific diagnosis could not be established.

The panel thought this case had some similarities to recently described cases of so-called splenic follicular lymphoma (FL).42 These latter cases have been described to have white pulp nodules composed predominantly of atypical, BCL2-, usually CD10- germinal center cells with a surrounding outer zone of monocytoid-appearing cells, similar to the current case. Plasmacytic differentiation, however, has not been described in these splenic FL cases. A recent study has shown that most cases of FL in the spleen are CD10+ and BCL2+, similar to nodal FL.43 However, additional studies are needed to clarify the nature of splenic FL and to assist in their distinction from MZLs with prominent and/or colonized germinal centers. Overall, a conservative approach to the diagnosis of SMZL was recommended by the review panel, and a diagnosis of splenic B-cell lymphoma/leukemia, unclassifiable, was preferred for cases that do not meet the established morphologic criteria.

**γ Heavy Chain Disease**

γ-HCD is defined as a lymphoplasmacytic neoplasm characterized by production of free IgG heavy chains without accompanying κ or λ light chains.44 Prior studies have indicated that the IgG heavy chains are abnormally truncated and fail to associate with light chains.45 γ-HCD is a rare entity, with only case reports and relatively small series described in the literature.46,47 In general, γ-HCD has been considered to represent a variant of LPL or at least a very similar lymphoproliferative disorder. However, most reports have contained little histologic detail.

Four cases of γ-HCD were submitted to the workshop. Consistent with prior reports, the patients were adults, all of whom were women. 3 had associated autoimmune histories (2 with systemic lupus erythematosus; 1 with autoimmune thyroiditis), and 1 had a coexisting large granular lymphocyte leukemia. Histologic material was available in 3 cases, and in 1 case consisted of flow cytometric data alone. The 2 lymph node–based cases and 1 salivary gland–based case showed effacement by a predominantly diffuse proliferation of small lymphocytes, plasmacytoid lymphocytes, and occasional plasma cells. Image 7. Two cases showed frequent residual germinal centers. Histiocytic clusters were prominent in 1 case.

By immunohistochemical studies, each case showed a CD20+ B-cell proliferation with IgG heavy chain+ plasma cells that lacked staining for κ or λ immunoglobulin light chain admixed with rare, scattered plasma cells with polytypic light chain expression. A key to making the diagnosis in these cases is recognition that many of the plasma cells identified by CD138 or IgG heavy chain stains are lacking κ and λ. If one were to perform κ and λ stains alone, the presence of the light chain negative plasma cell population might be missed. κ and λ in situ hybridization stains performed on 3 cases were also negative in the atypical IgG+ plasma cells. Clonality was
Image 7

(Case 146) Lymph node involvement by γ heavy chain disease. **A**, The lymph node displays reactive germinal centers with an expanded interfollicular proliferation (H&E). **B**, The interfollicular regions contain small lymphocytes, plasmacytoid lymphocytes, plasma cells, and occasional large cells (H&E). **C**, A CD20 stain shows few positive cells in the interfollicular areas. **D**, Numerous CD138+ cells are present. **E**, The plasmacytoid cells and plasma cells are positive for IgG. **F**, λ (left) and κ (right) stains show only rare positive cells.
confirmed by PCR studies for immunoglobulin heavy chain and/or κ light chains in all cases.

Additional studies are clearly needed to further characterize the spectrum of morphologic findings in γ-HCD and to establish whether this truly represents a unique lymphoproliferative disorder or whether γ-HCD should be considered simply a variant of otherwise typical MZLs or LPLs. These cases illustrate the importance of performing immunoglobulin heavy chain stains in the workup of lymphoplasmaocytic neoplasms and comparing results with those seen in light chain stains. Protein electrophoresis and immunofixation studies remain required to definitively diagnose γ-HCD.

HCV-Associated MC

One case of HCV-associated MC was submitted to the workshop (case 70). The patient was a 59-year-old man with a prior diagnosis of HCV who had fatigue, arthralgias, purpura, and elevated cryoglobulin levels (2,122 μg/mL; reference range, 0-50 μg/mL). Bone marrow biopsy and flow cytometry showed a clonal B-cell proliferation (12% of total cells analyzed) expressing CD19, CD20, and κ light chains and lacking CD5, CD10, and CD23. Immunohistochemical stains confirmed a mildly increased, interstitial infiltrate of B cells. Image 8.

The spectrum of lymphoproliferative disorders associated with HCV infection includes MC, MZLs (including MALT lymphoma and SMZL), and LPL.48-50 By definition, a clonal proliferation is present in all cases of MC, but there have been relatively few reports of the morphologic findings in these cases. Flow cytometry in these cases often demonstrates a clonal memory B-cell population that expresses IgM and CD27 with absence of CD5 and CD10.51 Classification of this clonal proliferation may be challenging, especially in the absence of complete clinical information. These findings may raise consideration of an SMZL or other disseminated MZL. Flow cytometry in these cases often demonstrates a clonal memory B-cell population that expresses IgM and CD27 with absence of CD5 and CD10.51 Classification of this clonal proliferation may be challenging, especially in the absence of complete clinical information. These findings may raise consideration of an SMZL or other disseminated MZL. Alternatively, because MC is due to production of a clonal IgM protein, the possibility of an LPL might also be considered. In the absence of significant splenomegaly, adenopathy, or distinct B-cell aggregates in the bone marrow, cases of MC are perhaps best considered to represent a precursor lesion, analogous to monoclonal B-cell lymphocytosis. Because symptoms in MC are generally secondary to the presence of cryoglobulins rather than to lymphomatous disease and because treatment of HCV may abrogate clinical symptoms, these cases should not be overdiagnosed as overt lymphomas that may lead to unnecessary therapy. Additional studies are needed to define criteria to distinguish between MC and MZLs or LPL.


