Mantle Cell Lymphoma—An Entity Comes of Age

By Dennis D. Weisenburger and James O. Armitage

In the mid-1970s, Berard et al.1-4 coined the term lymphocytic lymphoma of intermediate differentiation to describe a group of non-Hodgkin’s lymphomas (NHLs) that were not readily classifiable as either well-differentiated (small lymphocytic) or poorly differentiated (small cleaved cell) lymphoma. In lymph node sections, the tumors usually had a diffuse pattern of growth and were composed of a mixture of small lymphoid cells, some with round nuclei like those of small lymphocytic lymphoma and others with indented and cleaved nuclei like those of small cleaved cell lymphoma. Thus, the term intermediate was used to describe the intermediate morphologic appearance of the tumors. About the same time, Lennert et al.5-7 described a similar-appearing lymphoma, termed centrocytic, which was characterized by a predominance of irregular and cleaved lymphoid cells. Early immunologic studies of these tumors revealed a B-cell phenotype with the neoplastic cells showing moderate to intense staining for monoclonal surface Ig.3,4,7 Cytochemical stains for surface alkaline phosphatase suggested to Berard et al.3,4 that intermediate lymphocytic lymphoma corresponded to the cells of primary lymphoid follicles and the mantle zones of secondary follicles, whereas Lennert et al.5-7 believed that centrocytic lymphoma was a germinal center cell lymphoma.

In the early 1980s, Weisenburger et al.8 and Palutke et al.9 described a distinctive type of follicular lymphoma that was characterized by the proliferation of atypical small lymphoid cells in wide mantles around benign germinal centers. Weisenburger et al.10,11 coined the term mantle zone lymphoma for this entity and suggested that it represented the follicular counterpart of diffuse intermediate lymphocytic lymphoma.

More recent studies, which are detailed herein, have characterized all of these various lymphomas clinically, and at the molecular level, and have led to the conclusion that they represent a closely related spectrum of tumors that corresponds to lymphocytes in the primary lymphoid follicles and mantle zones of secondary follicles. Thus, the term mantle cell lymphoma (MCL) is now the accepted name for this group of lymphomas.11,12

Pathologic Features

The pathologic features of MCL have been refined and the histologic spectrum of the disease has been expanded in recent years through the use of immunologic, cytogenetic, and molecular techniques. A number of large, well-studied series with detailed descriptions of the pathology of the MCL have been published.13,14

Lymph nodes. The NHLs of mantle cell type usually consist of atypical small lymphoid cells and have either a nodular or diffuse pattern of growth, or a combination of the two patterns. Nodularity is present, at least focally, in approximately 30% of cases of MCL at the time of initial diagnosis. Early in the course of disease, nodular MCL may have a distinctly nodular or a vaguely nodular growth pattern at low magnification. In nodular MCL, some or many of the nodules may consist of follicles with reactive germinal centers surrounded by broad and expansive mantles of small lymphoid cells (Fig 1), the so-called mantle zone pattern.8,10 However, in such cases some neoplastic nodules without germinal centers, which mimic primary follicles, are also present. In other cases, these latter nodules may predominate or be present exclusively (Fig 2), and the process may be confused with a follicular center cell lymphoma of the small cleaved cell type. Later in the course of disease, invasion and obliteration of the reactive germinal centers and interfollicular areas by neoplastic cells results in a diffuse pattern of growth. Residual vague nodularity may be seen in such cases, and naked germinal centers lacking a normal lymphocyte cuff are found within the diffuse areas in approximately one quarter of the cases.

Cytologically, MCL usually consists of a monotonous population of atypical small- to medium-sized lymphoid cells with irregular and indented nuclei, moderately coarse chromatin, inconspicuous nucleoli, and scant cytoplasm (typical “intermediate” cytology). Small round lymphocytes, some of which are T cells, are admixed in variable numbers, and neoplastic cells with cleaved nuclei are often present as well. However, cases of MCL with predominantly round nuclei or only slight nuclear irregularity, and cases with...
markedly angulated and cleaved nuclei ("centrocytic" cytology) or even cerebriform nuclei do occur. Although the neoplastic lymphoid cells show a spectrum of nuclear irregularity from case to case, ranging from slight to marked, the cells usually show little variation in an individual neoplasm. In about 20% of cases of MCL, the neoplastic cells are larger than usual and have more finely dispersed nuclear chromatin and small nucleoli. Such cases have been referred to as large cell ("anaplastic centrocytic") or blastic variants of MCL. Sometimes, a mixture of atypical small cells and larger blastic cells is present, imparting a more pleomorphic cytologic picture. In other cases, the blastic cells are quite monotonous, ranging from medium to large in size, with very fine chromatin and multiple small nucleoli ("centrocytoid centroblastic" cytology). Thus, the diversity of morphologies seen in different cases of MCL is broad, ranging from small cells with round or slightly irregular nuclei at one end of the spectrum to large transformed cells with distinct nucleoli at the other end. The cytologic spectrum of MCL is shown in Fig 3.

In general, large transformed lymphoid cells with vesicular nuclei and prominent nucleoli (large noncleaved cells or centroblasts) are not seen in the lymphocytic forms of MCL, and plasma cells are usually absent or only present in small numbers and polyclonal in nature. The mitotic rate is generally low in the lymphocytic forms of MCL, but an increased mitotic rate is usually seen in the pleomorphic and blastic variants and is often accompanied by admixed benign histiocytes. These rather distinctive histiocytes have abundant pink cytoplasm and may contain phagocytized cellular debris.

Histologic progression from a nodular pattern to a diffuse pattern may be evident in a subsequent biopsy specimen, and progression from lymphocytic to blastic cytology with a high mitotic rate is not uncommon. Norton et al. noted histologic transformation to blastic cytology upon rebiopsy in 17% of their cases of MCL, and found blastic cytology in 70% of their cases at autopsy. However, transformation of MCL to the more common forms of diffuse large cell lymphoma is a rare event.

Cytology, peripheral blood (PB), and bone marrow (BM).
In lymph node touch preparations and other cytologic specimens, the neoplastic cells are small to medium sized, with irregular, indented, and cleaved nuclear contours, moderately clumped (smudged) to more finely dispersed chromatin, one or more conspicuous nucleoli, and small to moderate amounts of cytoplasm (Fig 4). Larger cells with round nuclei, fine chromatin, prominent nucleoli, and moderate amounts of basophilic cytoplasm are seen in the blastic variants of MCL. Smears of involved BM and PB generally reflect the lymphoid population present in the lymph nodes. The neoplastic cells in the blood and BM of a given patient may be quite heterogeneous in appearance (Fig 5). In BM sections, the neoplastic cells may infiltrate in either a focal, often paratrabeicular, pattern or a diffuse pattern. However, one should not make a diagnosis of MCL based on the examination of PB or BM alone because of the lack of precise criteria for such a diagnosis. However, immunologic studies by flow cytometry may be very useful in the diagnosis of such specimens.

Other organs. Involvement of other organs by MCL is not uncommon because the patients usually have advanced-
stage disease at the time of diagnosis. The spleen is often enlarged, particularly in those with the nodular (mantle zone) type. Microscopically, the white pulp areas are markedly expanded by a proliferation of atypical lymphoid cells, and reactive-appearing germinal centers may be present in these areas. Liver involvement is common and is characterized by atypical portal lymphoid infiltrates. Involvement of other extranodal sites is also common. Extranodal sites that are most likely to be involved primarily or as part of a disseminated process include the gastrointestinal (GI) tract and Waldeyer’s ring (20% to 30% of cases). GI involvement as multiple lymphomatous polyposis, often accompanied by a large localized mass, has been reported, but is not entirely specific for MCL.

IMMUNOLOGIC FEATURES

The immunohistologic features of MCL reveal a characteristic phenotype. In frozen sections, the cells have monoclonal B-cell phenotype, almost always bearing surface IgM and often sIgD. Surface IgG is expressed along with sIgM in about 20% of cases. The κ to λ light ratio is reversed in MCL, with about 60% of cases expressing monoclonal λ light chains, and the residual germinal centers are polyclonal. The neoplastic cells also stain for a variety of pan-B-cell antigens (CD19, 20, 22, and 24) and HLA-DR antigen. Interestingly, the cells usually have the pan-T-cell antigen CD5 on the surface and are negative for CD10 (CALLA) antigen. The neoplastic cells may also bear the T-cell–associated antigens CD43 and Leu8, but fail to stain for other pan-T-cell antigens. The cells are usually also negative for CD23 antigen. Antibodies to dendritic reticulum cells reveal large aggregates of these cells in cases with a nodular or mantle zone pattern, whereas a more sparse and irregular meshwork of dendritic cells is usually found in diffuse areas. Cases of blastoid MCL are less likely to express sIgD, CD5, and CD43, and may express CD10 antigen. The phenotype of MCL is remarkably similar to that of small lymphocytic lymphoma and chronic lymphocytic leukemia, except for more intense sIg and CD20 staining and lack of CD23 expression in MCL. Studies of cellular proliferation rates in MCL have generally found low rates in the lymphocytic forms and high rates in the blastoid variants, but with considerable overlap.

CYTOGENETIC AND MOLECULAR GENETIC FEATURES

The characteristic cytogenetic abnormality in MCL is the t(11;14)(q13;q32), which is seen in the majority of cases. Variant translocations involving the 11q13 breakpoint have also been reported, whereas the presence of trisomy 12 appears to be a secondary abnormality. The presence of a complex karyotype with hyperdiploidy has been associated with large atypical cells, and may suggest a more aggressive clinical course in MCL. However, the t(11;14)(q13;q32) also occurs, albeit infrequently, in other types of NHL, lymphocytic leukemia, and multiple myeloma. Therefore, cytogenetic findings need to be carefully correlated with the pathologic and immunologic features to confirm a diagnosis of MCL.

The molecular counterpart of the t(11;14) involves an error in V-D-J joining during Ig heavy-chain gene rearrangement, resulting in the movement of a putative cellular oncogene adjacent to the bcl-1(11q13) breakpoint into proximity of the enhancer region of the Ig heavy-chain gene(14q32). Breaks in the latter region are thought to occur during early B-cell development and are mediated by the recombinase system, whereas 11q13 appears to be a common fragile site. The breakpoints in the bcl-1 locus are not tightly clustered, although 30% to 40% of cases of MCL have breaks in the major translocation cluster (MTC) region(Fig 6). However, using multiple probes including those for a number of minor breakpoint regions, a variety of investigators have detected clonal rearrangements in 50% to 70% of patients with MCL. Recently, a polymerase chain reaction (PCR) assay has been developed and used to detect most of the breaks in the MTC region. This assay may also be used on DNA extracted from paraffin-embedded tissues. The use of chromosome 11 paints and fluorescent in situ hybridization (FISH) to detect the t(11;14) in interphase cells of MCL has also been reported recently. Both the PCR and FISH techniques will be useful to detect minimal residual disease in MCL.

The putative oncogene deregulated by the t(11;14) was recently identified by two groups and is located approximately 120 kb telomeric from the MTC breakpoint (Fig 6). The gene was named PRAD1 because of its original recognition in parathyroid adenoma, but has been officially named CCND1. The gene encodes for cyclin D1 and is overexpressed in nearly all cases of MCL, whereas it is expressed only rarely in other forms of hematopoietic cancer. Because overexpression of this gene at the RNA level has also been noted in most cases of MCL without detectable bcl-1 rearrangements, additional minor breakpoint sites outside of those detected by the available probes are likely to be involved in the translocation of chromosome 11q13. Alternatively, deregulation could occur by mutation or deletion of negative regulator elements adjacent to the gene, or extra copies of the gene may result in its overexpression. All of the known breakpoints leave the CCND1 coding region structurally intact and result in increased pro-
tein expression. In some cases, loss of 3’ end regulatory sequences may also increase the half-life of cyclin D1. Recently, antibodies to cyclin D1 which work on paraffin-embedded material have been shown to be highly sensitive and specific for MCL, and should be very useful diagnostically when they become commercially available. Alternatively, in situ hybridization detection of cyclin D1 mRNA in cytopreps or paraffin tissues can be used to elucidate the nature of diagnostically difficult cases.

The mechanism by which cyclin D1 overexpression facilitates lymphomagenesis is not yet well understood, but its key role in cell-cycle regulation and the progression of cells through the main commitment checkpoint in G1 to S phase is certainly important. Overexpression of cyclin D1 results in a shortened G1 phase, probably through its physical interaction with the tumor-suppressor retinoblastoma protein (RB). Cyclin D1 binds to and activates important enzymes called cyclin-dependent kinases (mainly CDK4 and CDK6), whose activity is needed to propel cells through the G1 checkpoint. Cyclin D1-CDK4 complexes then bind to and hyperphosphorylate RB, which in turn prevents RB from binding important transcription factors such as E2F. Thus, the growth-restraint effect of RB via its binding of transcription factors is removed, and the cells are propelled into S phase (Fig 7).

Mutations of the tumor-suppressor p53 gene have recently been reported in aggressive variants of MCL. This gene regulates the expression of p21 protein, which is an important universal inhibitor of cyclin-CDK complexes, including cyclin D-CDK4. Thus, mutations of the p53 gene with loss of this inhibition could further enhance the effects of overexpressed cyclin D1. The normal p53 gene acts as a molecular monitor of the genome. If DNA is damaged, p21 protein accumulates and switches off replication to allow extra time for DNA repair. If the repair fails, p53 may trigger cell suicide by apoptosis. However, tumor cells in which p53 is inactivated by mutation cannot carry out this arrest and are genetically unstable. Such cells will accumulate mutations and chromosomal rearrangements at an increased rate, thus leading to the rapid selection of highly malignant clones. Thus, p53 also plays a critical role at the G1 checkpoint, and mutations of p53 are important in the progression of MCL.

Evidence has recently accumulated that CCND1 can function like an oncogene by causing abnormalities of cellular growth control, cell-cycle progression, and gene expression, as well as malignant transformation. Studies using transgenic mice have shown that CCND1 cooperates with myc genes in the generation of B-cell lymphomas, although CCND1 was not oncogenic by itself. However, these studies showed subtle alterations in cell-cycle progression and the number of BM B cells due to CCND1 overexpression. Activation of cyclin D genes by proviral insertions in murine lymphomas has also been reported. Recently, cyclin D1 was shown to induce mammary hyperplasia and carcinoma in a different transgenic model. Thus, it appears that CCND1 is a bona fide oncogene whose activity appears to depend on the specific cell type as well as specific cooperating partner genes to induce tumors. Further elucidation and study of such gene interactions is needed in MCL.

NORMAL CELLULAR COUNTERPART

Currently, the various types of B-cell neoplasia are thought to represent cells arrested at various stages in the normal differentiation scheme. The histologic and immunologic features of MCL suggest that the neoplastic cells correspond to normal, naive B lymphocytes that home to and reside in primary lymphoid follicles and the mantle zones of secondary follicles. These cells seem to correspond phenotypically to a major population of fetal B cells that leave the BM and form the primary lymphoid follicles in the lymph nodes and spleen. At birth, 68% of cord blood B cells and approximately half of PB B cells are CD5+. These cells are morphologically similar to the cells of MCL. In the adult, CD5+ B cells circulate in small numbers and are found in the inner area of mantle zones of lymphoid follicles. Recently, normal mantle cells were shown to express a diverse repertoire of unmutated Ig heavy chain variable region genes, as one would expect of naive pre-germinal center B cells. Identical findings have also been reported in MCL. Furthermore, CD5+ B cells can be induced to differentiate to CD5+ cells with the immunologic features of germinal center cells. Thus, the cells of MCL appear to correspond to precursor cells of the normal germinal center reaction. The possibility that some cases of MCL arise from a subset of mantle zone lymphocytes with the immunologic features of marginal zone cells has been suggested by some investigators.

DIFFERENTIAL DIAGNOSIS

A diagnosis of MCL with a mantle zone pattern may be difficult to make when incomplete obliteration of the normal lymph node architecture and numerous benign-appearing germinal centers are present. However, the presence of wide follicular mantles in mantle zone lymphoma is distinctly different from the thin mantles found in most cases of reactive follicular hyperplasia. In the spleen, involvement of the red pulp by lymphoma is a helpful diagnostic feature. However, in lymph nodes, mantle zone hyperplasia and angiofollicular lymphoid hyperplasia of the hyaline-vascular type

Fig 7. Schematic diagram showing the functional interrelationships of cyclin D1. (Reprinted with permission.)
Differentiating the various entities (Table 1). The nodular and cleaved as those of follicular center cell lymphoma. How-
and cleaved cells exit the neoplastic mantle zone lymphoma because they arise from germinal centers without diffuse areas of involvement. Imm-
monoclonality, and CD5 and CD43 positivity, Bhan% have described a rare form of follicular center cell lymphoma in which small cleaved cells exit the neoplastic mantle zone lymphoma. However, the presence of pseudofollicular proliferation centers and paraimmunoblasts in small lymphocytic lymphoma are useful differential features because they do not occur in MCL. Perry et al.99 have also shown that lymphocytic lymphomas composed of cells with irregular nuclei, but having pseudofollicular proliferation centers, should be classified as small lymphocytic lymphoma for clinical purposes. The immunophenotypes of MCL and small lymphocytic lymphoma are similar, but the presence of numerous dendritic reticulum cells and the absence of CD23 antigen in MCL are useful diagnostic features.

A variety of NHLs may also be confused with the lymphomas of mantle cell origin. However, immunohistochemical and cytogenetic or molecular studies may be very useful in differentiating the various entities (Table 1). The nodular (primary follicular) form of MCL may be difficult to differentiate from follicular small cleaved cell lymphoma. However, the cells of MCL are usually not as markedly angulated and cleaved as those of follicular center cell lymphoma. Also, large transformed cells are usually absent in MCL, although residual large cells from invaded benign germinal centers may occasionally confuse the issue. Harris and Bhan98 have described a rare form of follicular center cell lymphoma in which small cleaved cells exit the neoplastic mantle zone centers and accumulate in the adjacent mantle zones. However, such cases should not be considered as mantle zone lymphomas because they arise from germinal center cells. In difficult cases, immunohistochemical stains can be used to separate follicular center cell lymphoma from MCL by the fact that the former has monoclonal, CD10+ germinal centers and CD5+ mantle zones, whereas polyclonal germinal centers and monoclonal, CD5+ mantle zones are seen in nodular MCL. Immunologic studies may also be helpful in separating diffuse MCL from diffuse small cleaved follicular center cell lymphoma, which is usually CD5− and CD10+, and often exhibits Ig heavy-chain switching to a more mature phenotype.97 Also, transformed large cells, and small cells with the markedly elongated and twisted nuclei of follicular center cell lymphoma, are generally absent in diffuse MCL.

Table 1. Phenotypes of Various B-Lymphocytic Lymphomas

<table>
<thead>
<tr>
<th>Subtype</th>
<th>sig</th>
<th>clg</th>
<th>CD6</th>
<th>CD10</th>
<th>CD23</th>
<th>CD43</th>
<th>DRC</th>
<th>Cytogenetics</th>
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<tbody>
<tr>
<td>MCL</td>
<td>M ≤ D</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>t(11;14)(q13;q21)</td>
</tr>
<tr>
<td>Follicular center cell lymphoma</td>
<td>G ≤ M</td>
<td>−</td>
<td>−</td>
<td>+/−</td>
<td>+/−</td>
<td>−</td>
<td>+</td>
<td>t(14;18)(q32;q21)</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma/CLL</td>
<td>M ≥ D</td>
<td>−/−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Trisomy 12</td>
</tr>
<tr>
<td>Monocytoid B-cell lymphoma</td>
<td>M</td>
<td>−/−</td>
<td>−</td>
<td>−</td>
<td>−/−</td>
<td>−</td>
<td>−</td>
<td>Trisomy 3</td>
</tr>
<tr>
<td>Mucosa-associated lymphoma</td>
<td>M</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Trisomy 3</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>M</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: sig surface immunoglobulin; clg, cytoplasmic immunoglobulin; DRC, dendritic reticulum cell network; CLL, chronic lymphocytic leukemia; +, >80% positive; +/-, >50% positive; −/+ <50% positive; −, <20% positive; NA, no common abnormality reported.

(Castleman’s disease) are two uncommon reactive processes that may be difficult to distinguish from mantle zone lymphoma. Mantle zone hyperplasia usually occurs as an isolated, small node in the neck of a young individual. In mantle zone hyperplasia, the follicles are usually localized to the cortex of the node, and the architectural effacement and diffuse areas of involvement characteristic of lymphoma are lacking. Angiofollicular lymphoid hyperplasia also usually presents in young individuals, but as a large and localized mass, and is characterized by typical hyaline-vascular germinal centers without diffuse areas of involvement. Imm-
munohistochemical stains may be very helpful in distinguish-
ing mantle zone lymphoma from these reactive pro-
cesses. The monoclonality, and CD5 and CD43 positivity, of the neoplastic cells clearly separate mantle zone lymphoma from the follicular, mantle zone, and angiofollicu-
lar hyperplasias. This rule is also valid for separating diffuse MCL from diffuse reactive lymphoid proliferations of B-cell type.

A variety of NHLs may also be confused with the lymphomas of mantle cell origin. However, immunohistochemical and cytogenetic or molecular studies may be very useful in differentiating the various entities (Table 1). The nodular (primary follicular) form of MCL may be difficult to differentiate from follicular small cleaved cell lymphoma. However, the cells of MCL are usually not as markedly angulated and cleaved as those of follicular center cell lymphoma. Also, large transformed cells are usually absent in MCL, although residual large cells from invaded benign germinal centers may occasionally confuse the issue. Harris and Bhan98 have described a rare form of follicular center cell lymphoma in which small cleaved cells exit the neoplastic mantle zone centers and accumulate in the adjacent mantle zones. However, such cases should not be considered as mantle zone lymphomas because they arise from germinal center cells. In difficult cases, immunohistochemical stains can be used to separate follicular center cell lymphoma from MCL by the fact that the former has monoclonal, CD10+ germinal centers and CD5+ mantle zones, whereas polyclonal germinal centers and monoclonal, CD5+ mantle zones are seen in nodular MCL. Immunologic studies may also be helpful in separating diffuse MCL from diffuse small cleaved follicular center cell lymphoma, which is usually CD5− and CD10+, and often exhibits Ig heavy-chain switching to a more mature phenotype.97 Also, transformed large cells, and small cells with the markedly elongated and twisted nuclei of follicular center cell lymphoma, are generally absent in diffuse MCL.

Interfollicular small lymphocytic lymphomas may encroach on and invade reactive follicles and produce a pseudo-

mantle zone pattern.98 This pattern is characterized by reactive germinal centers with thin, residual mantle zones that are surrounded by the neoplastic infiltrate. However, the predominance of small lymphocytes with uniformly round nuclei and the presence of pseudofollicular proliferation centers and paraimmunoblasts in small lymphocytic lymphoma are useful differential features because they do not occur in MCL. Perry et al.99 have also shown that lymphocytic lymphomas composed of cells with irregular nuclei, but having pseudofollicular proliferation centers, should be classified as small lymphocytic lymphoma for clinical purposes. The immunophenotypes of MCL and small lymphocytic lymphomas are similar, but the presence of numerous dendritic reticulum cells and the absence of CD23 antigen in MCL are useful diagnostic features.

A pseudo-mantle zone pattern may also be seen in mono-
cytoid B-cell lymphoma, centrocyte-like B-cell lymphoma occurring in mucosa-associated lymphoid tissues, and per-
ipheral T-cell lymphoma composed of atypical small lymphoid cells. These lymphomas arise in the parafollicular or interfollicular regions and may secondarily invade reactive lymphoid follicles. Each of these lymphomas has distinctive histologic and immunologic features that are useful in the differential diagnosis (Table 1). However, the presence of lymphoepithelial lesions is not useful in differentiating MCL from centrocyte-like lymphoma of mucosa-associated lymphoid tissue, because they have also been described in MCL.24,25,100 Pileri et al.101 have described cases of apparent "mantle zone" lymphoma of the lymphocytic type with plasma cell differentiation. However, it is not clear whether these investigators are describing interfollicular lymphoplasmacytoid/cytic lymphomas with a pseudo-mantle zone pattern or a rare form of MCL with plasma cell differentiation.

The blastic variants of MCL may sometimes be confused with B-lymphoblastic lymphoma102 or granulocytic sarcoma, although the chromatin pattern is usually somewhat more coarse in blastic MCL. Immunologic studies are usually helpful in this regard, because blastic MCL is surface Ig− and CD5+, and terminal deoxynucleotidyl transferase (t(11;14))−, whereas B-lymphoblastic lymphoma is CD5+, usually surface Ig+, and tdt+. The presence of CD10 is not helpful.
MANTLE CELL LYMPHOMA

because it may be expressed in either entity. In addition to the above features, a number of myeloid markers including myeloperoxidase, lysozyme, and specific esterase will clearly delineate granulocytic sarcoma from MCL.

Although MCL may be diagnosed in extranodal sites, such as the GI tract, one should hesitate to make a primary diagnosis of MCL in extranodal sites such as the BM, liver, or soft tissue, because of the nuclear irregularities that may occur as a result of the surrounding fibrous tissue reaction. Such cases are better diagnosed as lymphocytic lymphoma, not further classified, if corroborating evidence for MCL cannot be obtained. Similarly, one should not make a diagnosis of MCL based on BM or PB smears alone, because criteria for such a diagnosis have not been well defined. A lymph node biopsy with immunologic studies is often necessary to categorize such cases precisely, although flow cytometric and molecular studies of blood and BM may also be useful.21,22,27

CLINICAL FEATURES

Mantle cell lymphoma comprises 2.5% to 4.0% of all NHLs in the United States, whereas higher rates of 7% to 9% are found in Europe. A number of detailed studies have defined the clinical features of MCL (Table 2).15,17-19,103-109 Patients with MCL have a median age of approximately 60 years, and males predominate. Patients generally present with advanced (stage III/IV) disease, usually with generalized lymphadenopathy and BM and liver involvement, but fewer than one half of the patients have systemic (B) symptoms. Splenomegaly is present at initial diagnosis in approximately 60% of the patients. In the nodular (mantle zone) type, 80% of the patients have splenomegaly, which may be massive. Other extranodal sites are also frequently involved, particularly the gastrointestinal tract and Waldeyer’s ring (20% to 30% of cases). A particularly striking extranodal presentation is multiple lymphomatous polyposis of the intestine, which should suggest a diagnosis of MCL. Mild anemia is not uncommon at presentation, whereas thrombocytopenia occurs in fewer than 15% of the patients. A PB lymphocytosis of >4,000/μL occurs in 20% to 40% of the cases, but absolute counts >20,000/μL are uncommon. Hypergamma globulinemia, a monoclonal gammopathy, and a positive Coombs’ test are also decidedly uncommon.

TREATMENT AND SURVIVAL

Mantle cell lymphoma is a vexing and increasingly frequent problem for oncologists. The disease brings together the worst characteristics of high-grade and low-grade lymphomas; ie, the course is not indolent and the disease is rarely curable. The median survival of patients with MCL has ranged between 3 and 4 years in large series,13,15,17-19,103,104,106-109 This is significantly shorter than the survival of the patients with similar forms of lymphoma (Fig 8). In two detailed studies,14,15 patients with a nodular (mantle zone) pattern had a significantly longer median survival (77 to 88 months) when compared to those with diffuse MCL (30 to 33 months) (Fig 9). The prognostic significance of a predominantly nodular pattern has recently been confirmed by others.19,107,108,111 With the use of noncurative, pre-first generation combination chemotherapy, which usually did not contain doxorubicin, various investigators obtained complete remission (CR) rates of

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Table 2. Clinical Features of MCL at Initial Presentation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>60 yr</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>4:1</td>
</tr>
<tr>
<td>Generalized lymphadenopathy</td>
<td>90%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>60%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>30%</td>
</tr>
<tr>
<td>PB lymphocytosis</td>
<td>30%</td>
</tr>
<tr>
<td>BM infiltration</td>
<td>80%</td>
</tr>
<tr>
<td>GI involvement</td>
<td>20%</td>
</tr>
<tr>
<td>Waldeyer’s ring involvement</td>
<td>10%</td>
</tr>
<tr>
<td>Ann Arbor Stage III/IV</td>
<td>90%</td>
</tr>
<tr>
<td>B symptoms</td>
<td>40%</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>30%</td>
</tr>
<tr>
<td>Poor performance status</td>
<td>20%</td>
</tr>
<tr>
<td>Elevated lactate dehydrogenase</td>
<td>40%</td>
</tr>
<tr>
<td>Elevated β₂-microglobulin</td>
<td>55%</td>
</tr>
</tbody>
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Fig 8. Overall survival of patients with MCL compared with those having Working Formulation (WF) types A through E. (Reprinted with permission.)

Fig 9. Overall survival of patients with MCL having a mantle zone pattern compared with those with a diffuse pattern. (Reprinted with permission.)
20% to 40%. Meusers et al reported a CR rate of 58% when using a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), but few long-term remissions or cures have been reported in any series because of disease recurrence and progression. Zucca et al have reported a benefit from aggressive chemotherapy in a subset of patients with good prognostic indicators. Teodorovic et al recently reported a CR rate of 52% for patients treated with aggressive chemotherapy and suggested that improved survival may be achieved if a CR after CHOP-like aggressive chemotherapy, also containing bleomycin, is obtained. In elderly patients, less aggressive therapy such as cyclophosphamide, vincristine, and prednisone (CVP) may be justified. Therapeutic experience with the purine analogues, fludarabine and 2-CDA, and interferon has been disappointing. Although a small proportion of patients may benefit from observation only, Bookman et al found that CRs could not be obtained when such patients were later treated for progressive symptomatic disease. However, most studies have shown that patients who achieve a CR have a longer survival than those who do not achieve a CR, but few patients are cured. Because the long-term prognosis of patients receiving conventional therapy for MCL is rather poor, the use of aggressive combination chemotherapy with stem cell transplantation for younger patients has been suggested. Stewart et al recently treated nine such patients with high-dose therapy and stem cell transplantation, and three were progression-free at 7, 12, and 25 months posttransplantation. However, longer follow-up of greater patient numbers will be required to determine whether high-dose therapy can overcome the chemoresistance and increase the cure rate of MCL. The optimal timing for high-dose therapy may be early as part of frontline treatment.

A number of clinical and pathologic features are predictive of survival in MCL. The clinical features predicting a poor prognosis are generally the same as those found in other lymphoma subtypes and include advanced age and stage, B symptoms, poor performance status, PB lymphocytosis, elevated lactate dehydrogenase or β2-microglobulin levels, high risk with the International Prognostic Index (Fig 10), and failure to achieve a good clinical response to therapy. The pathologic features that predict a poor prognosis are a diffuse pattern, a high mitotic rate or proliferative fraction, blastic cytology, and p53 overexpression.

**TUMOR GRADE**

The Working Formulation divides the different subtypes of NHL into low-grade, intermediate-grade, and high-grade categories according to their median survivals, whereas the Kiel Classification uses only low-grade and high-grade categories based on cytologic features rather than survival. Because MCL was not well understood when the Working Formulation was prepared, it was not included as a category in the Working Formulation, although most cases of MCL were probably included in diffuse small cleaved cell lymphoma in that study. However, MCL is considered to be a low-grade lymphoma in the Kiel Classification. Based on the studies cited herein, we believe that the predominantly nodular (mantle zone) form of MCL composed of small lymphoid cells should be considered a low-grade lymphoma (median survival, >5 years), whereas diffuse MCL composed of small cells should be considered an intermediate-grade lymphoma (median survival, 3 years). However, the lymphocytic types of MCL are similar to other lymphomas of low-grade malignancy in that they are generally incurable, except for the uncommon case with low-stage disease. The blastic variants of MCL have cytologic features and proliferative rates similar to those of the high-grade lymphomas (small noncleaved and lymphoblastic) in the Working Formulation and, regardless of pattern, should probably be considered as such (median survival, <2 years). De novo cases of blastic MCL may be the most responsive to high-dose therapy and should probably be treated with curative intent. Future classifications of NHL should include MCL, with all of its various patterns and cytologies, so that future clinical studies can clearly delineate and further characterize this important entity.

**CONCLUSION**

Numerous recent studies have confirmed that MCL is a distinct clinicopathologic entity. The neoplastic cells of MCL appear to correspond to naive B cells that normally home to and reside in primary lymphoid follicles and the mantle zones of secondary follicles. As such, they correspond to a subset of normal follicular B cells that are thought to transform into germinal center cells in response to antigen. The relationship between the nodular (mantle zone) and diffuse lymphocytic forms of MCL is biologically analogous to the germinal center cell lymphomas of follicular and diffuse types, respectively, whereas the blastic forms of MCL are analogous to the transformed lymphomas arising in other low-grade lymphomas. New and better therapies are badly needed for this group of lymphomas, including further exploration of high-dose therapy with stem-cell rescue, immunotherapy with anti-shared idiotype monoclonal antibodies, radioimmunotherapy with 131I-labeled B-cell—spe-
cific antibodies,\textsuperscript{115} and innovative approaches which take advantage of cell-cycle checkpoints and proliferation controls.\textsuperscript{116,117} Until such progress is made, MCL will continue to be one of the worst forms of NHL, a clinically aggressive disease with little hope of a cure.

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