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Low Grade Lymphomas in the Elderly*

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ABSTRACT

Aging is considered to play an important role in the pathogenesis of non-Hodgkin's lymphoma (NHL). Recent epidemiological studies, both in the United States and worldwide, show an increasing incidence of NHL, with the increase also marked in the elderly population. Two hundred thirty-two patients with NHL, aged 60 years and older (44 percent female and 56 percent male), have been analyzed retrospectively. These patients represented 39 percent of all NHL cases seen over a seven-year period at a single institution. Among the elderly cases, 81 (35 percent) were classified as low-grade NHL, with 44 (19 percent) small lymphocytic lymphoma/chronic lymphocytic leukemia, 2 (1 percent) small lymphocytic lymphoplasmacytoid, 13 (6 percent) diffuse small cleaved including mantle cell, and 22 (9 percent) follicular small cleaved and mixed cell types. Although the indolent lymphomas are currently treated similarly, recent studies indicate differences in pathogenesis and survival among the classic subtypes. Also, several new low-grade clinicopathologic entities have been described. The clinical, morphologic, immunophenotypic, and genetic features of the classic and newer low-grade lymphomas are discussed.

Introduction

The overall incidence of non-Hodgkin's lymphoma (NHL) in the elderly has increased during the last few decades.[1,2] The average age-adjusted incidence of NHL in patients older than 65 years has been shown to be higher than in younger age groups.[2] The reason for the increased incidence of NHLs in the elderly population is not well understood. Aging is probably by itself one of the most important factors in the development of lymphomas.[3,4,5] The immunologic deficits.[6] T-cell proliferation abnormalities,[5] changes in immunoglobulin gene selection,[7] and decrease in cytokines[4] are some of the factors considered to play an important role. Long term exposure to environmental factors, including chemi-

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cals used in farming, forestry, building and painting, are also shown to be risk factors in the development of NHL.[8,9,10,11,12]

Although the low-grade NHLs are considered to be indolent, they are often fatal diseases. The response to conventional chemotherapy in patients 60 years of age and older is worse than in the younger population.[13] Although the various subtypes of low-grade NHLs are currently treated similarly, they represent lymphoid neoplasms with heterogeneous cellular origin, pathogenesis, morphologic features, and clinical behavior. Most of the indolent lymphomas seen in the US and Europe are tumors of B-cell origin.

The low-grade lymphomas in the Working Formulation (WF) classification system include small lymphocytic lymphoma/chronic lymphocytic leukemia (SSL/CLL), small lymphocytic lymphoma with plasmacytoid features (SLL,Pl), and follicular lymphoma, small cleaved cell and mixed cell types (FSC/M). In recent years, new low-grade B-cell lymphoma entities have been described. Examples of these disorders are mantle cell lymphoma, monocytoid B-cell lymphoma and lymphomas of mucosa associated lymphoid tissues (MALT), and splenic lymphoma with villous lymphocytes.

To illustrate the importance of low-grade NHLs in elderly patients, the results are briefly summarized of a retrospective analysis of 232 NHL patients aged 60 years and older, concentrating on the 81 patients (35 percent) diagnosed with indolent NHL. These lymphomas were classified according to the WF. Because of lack of adequate immunophenotypic and genotypic data in these cases, re-classification was not possible. Because of the common occurrence of low grade NHLs in elderly patients, it is particularly important for those who care for these patients to be familiar with major characteristics of these disorders. Thus, the clinical, morphologic, immunophenotypic, and genetic features of both the classic and newer low-grade NHLs are reviewed.

Patients and Methods

Clinical and pathologic data from 232 NHL patients 60 years of age and over were analyzed. These cases were extracted from a total of 593 cases of NHL registered at the H. Lee Moffitt Cancer Center (LMCC), Tampa, Florida, from January 1987 through May 1994. The cases were classified according to the Working Formulation of NHL for clinical usage.[14] Survival data were calculated by the Kaplan–Meier method. All patients underwent physical examination, routine laboratory testing, and staging according to the Ann Arbor criteria.[15] Eighty-one cases in patients 60 years of age and older were classified as indolent NHL, including SLL/CLL, SLL,Pl, FSC/M, and diffuse small cleaved (DSC) cell types.

Results and Discussion

In figure 1 is shown the distribution of the NHLs in patients 60 years of age and older according to the grades of the WF. Thirty-five percent were classified as low grade, 44 percent intermediate grade, and 11 percent were representative of mycosis fungoides/Sezary syndrome. Male patients were more common than female patients (M:F = 1.6:1). In figure 2 is shown the distribution of the indolent NHLs according to the WF. Most of the patients with indolent lymphomas presented with stage III or IV. The SLL/CLL was the most common low-grade lymphoma, followed by FSC/M. The survival of the older patients with indolent lymphomas was worse than in the younger NHL patient population (figure 3).

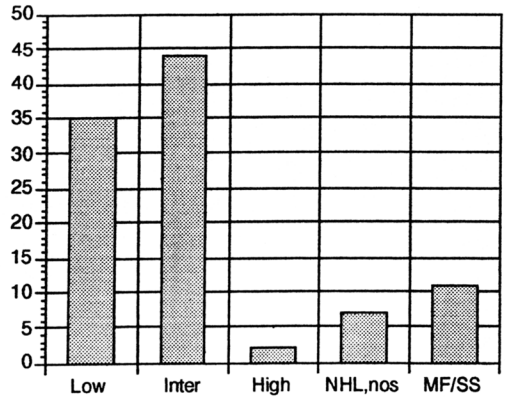

FIGURE 1. Percent of distribution of non-Hodgkin's lymphoma in patients 60 years of age and older seen at H. Lee Moffitt Cancer Center, 1987–1994, classified according to the Working Formulation: low, intermediate, and high grades; not otherwise specified (NOS); and mycosis fungoides/Sezary syndrome (MF/SS).

SMALL LYMPHOCYTIC LYMPHOMA/CHRONIC LYMPHOCYTIC LEUKEMIA

This is the most common indolent lymphoma. There has been a recent overall increase in the incidence rate of SLL/CLL.[16] One possible explanation for this

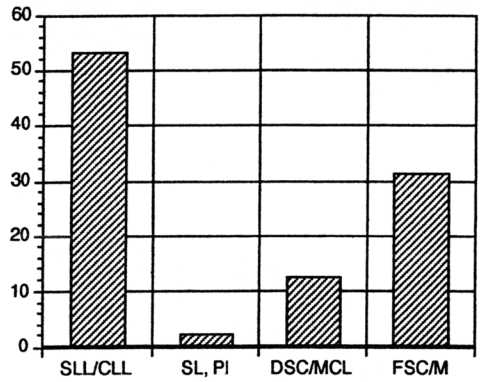

FIGURE 2. Percent of distribution of subtypes of indolent non-Hodgkin's lymphoma diagnosed at the H. Lee Moffitt Cancer Center, 1987–1994, according to the Working Formulation: small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL); small lymphocytic lymphoma with plasmacytoid features (SLL,Pl); diffuse small cleaved/mantle cell lymphoma (DSC/MCL); and follicular lymphoma, small cleaved cell and mixed cell types (FSC/M).

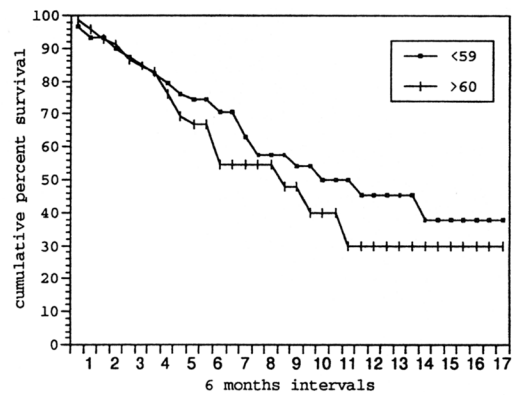

FIGURE 3. Overall survival of patients with low grade non-Hodgkin's lymphoma treated at H. Lee Moffitt Cancer Center and showing survival for two age groups ($p < 0.01$).

apparent increased incidence is the development of improved diagnostic criteria. There is a male predominance. The patients with nodal disease also generally show bone marrow involvement. The histologic features of lymph node involvement in SLL and CLL are identical.[17] In general, the lymph node architecture is effaced by diffuse infiltration of small, round lymphocytes with clumped chromatin and scanty cytoplasm (figure 4). Nodular growth is uncommon and should raise a suspicion of other diagnoses, Pseudoproliferation centers and paraimmunoblasts are good morphologic clues in support of SLL/CLL. The presence of an increased number of paraimmunoblasts indicates more aggressive clinical behavior.[18]

The most common chromosomal abnormalities are trisomy 12 and structural abnormalities of the long arms of chromosomes 13 and 14.[19,20] Although trisomy 12 is a common finding in CLL/SLL (up to 54 percent by fluorescent *in situ* hybridization [FISH] studies), it also occurs in other lymphomas.[21] The small lymphocytic lymphomas express CD19, CD20, CD22, CD23, and surface immunoglobulin, most commonly IgM and IgD types.[22] These neoplasms are characterized by expression of CD5 anti-

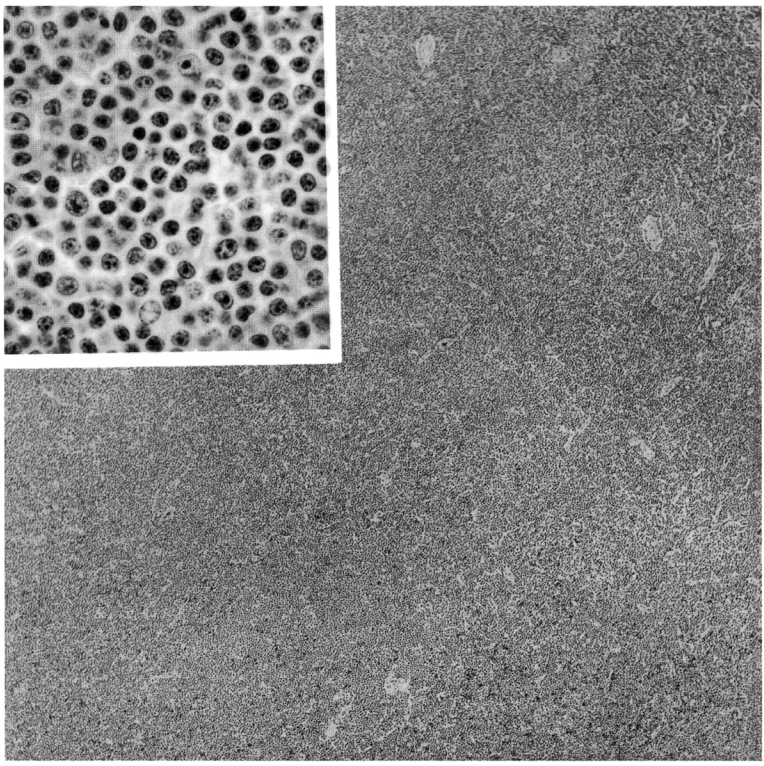

FIGURE 4. There is diffuse effacement of lymph node architecture, with pale growth centers, a characteristic pattern of small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). No residual germinal centers are present. At higher magnification, uniform infiltration of small round lymphocytes with scant cytoplasm admixed with larger cells with prominent nucleoli (paraimmunoblasts) is demonstrated. (H&E 40×, 400×).

gen.[23,24] The majority of the previously classified SLLs in extranodal sites are now thought to represent low-grade B-cell lymphomas of MALT. Although most SLLs show round to oval nuclei, occasional moderate nuclear irregularity can be seen and may raise a suspicion of mantle cell lymphoma. The CD23 is reported to be useful in distinguishing SLL/CLL from mantle cell lymphoma.[25] The level of expression of CD20 and surface immunoglobulin tends to be lower in SLL/CLL than mantle cell lymphoma.[26]

LYMPHOPLASMACYTOID LYMPHOMA

Only 2 of 82 patients in our study were classified in this category. Patients with this neoplasm usually present with clinical features of hyperviscosity (related to IgM hypergammaglobulinemia), organomegaly and anemia.[27] The median age is over 60 years.[27,28] Response rates to treatment are worse in patients older than 60 years.[27] Involved lymph nodes typically show diffuse or partial effacement by a proliferation of small round to ovoid lymphocytes, with admixed plasmacytoid lymphocytes and plasma cells (figure 5). Some neoplastic cells may show intranuclear inclusions (Dutcher bodies), and mast cells may be present. Immunophenotypic features include expression of B-cell markers CD19, CD20, and CD22. These cases usually lack CD5 and CD10 expression.[29,30] There is no reported consistent specific chromosomal abnormality associated with this lymphoma.

MARGINAL ZONE B-CELL LYMPHOMA (MONOCYTOID B-CELL LYMPHOMA)

Monocytoid B-cell lymphoma (MBCL) is currently referred to as marginal zone B-cell lymphoma in the newly proposed

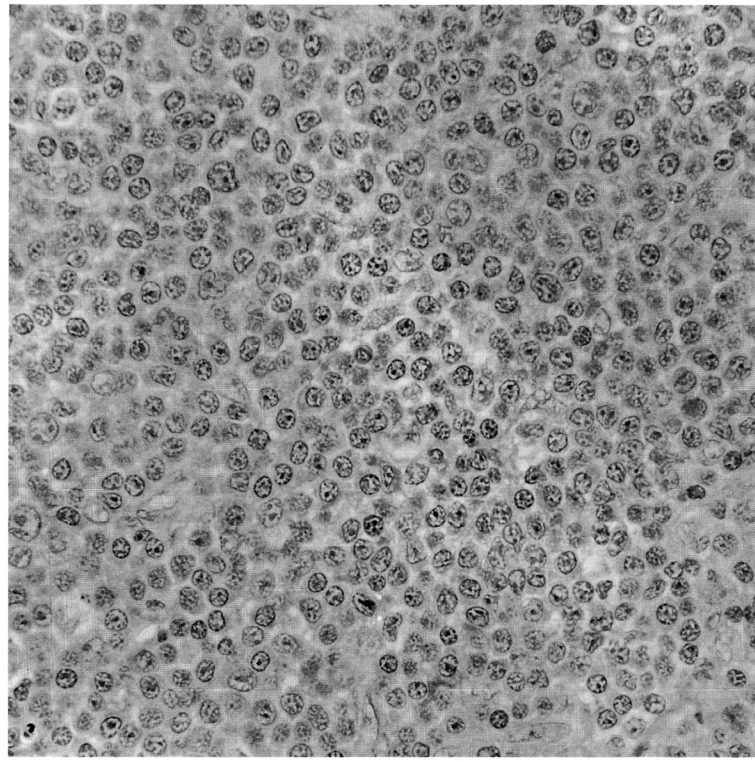

FIGURE 5. Small lymphocytic lymphoma with plasmacytoid features. Lymph node architecture is effaced by diffuse proliferation of plasmacytoid lymphocytes with moderately abundant cytoplasm. (H&E 400×).

European-American classification.[31] Extranodal marginal zone lymphomas frequently occur in patients with autoimmune disease such as Sjogren's syndrome. The median age of patients with monocytoid B-cell lymphomas is 65 years. Some of these neoplasms were probably previously classified as SLL/CLL or SLL/Pl. These lymphomas are characterized by the proliferation of monocytoid B-cells. The monocytoid B-cells consist of lymphocytes with abundant cytoplasm and irregular nuclei. Plasmacytoid differentiation is commonly present. Most low-grade lymphomas arising from mucosa-associated lymphoid tissue share many histologic, immunophenotypic, and clinical features with MBCL, and may represent an extranodal counterpart.[32,33]

One of the characteristic findings in involved lymph nodes is so called "inverted follicular appearance" owing to the expansion of neoplastic monocytoid B cells; the lighter staining neoplastic monocytoid B cells surround the darker staining normal germinal centers (figure 6). This is the inverse appearance of a normal lymph node in which the lighter staining germinal center is surrounded by the darker staining mantle zone.

Abnormalities of chromosome 3 and the t(11;18) translocation have been reported in MALT lymphomas; however, no specific abnormality has been reported for the nodal MBCLs. These tumors show absence of the bcl-1 [t(11;14)] and bcl-2 [t(14;18)] gene translocations.[34,35,36] The MBCLs are positive for B-cell markers CD19, CD20 and CD22. They are CD5, CD10, and CD23 negative, which help to differentiate them from other low-grade lymphomas.

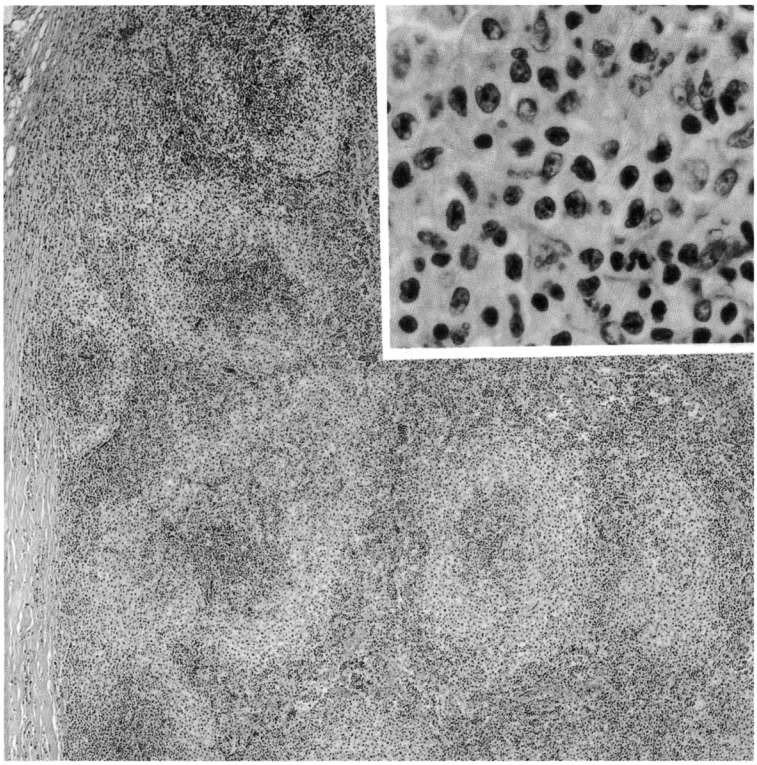

FIGURE 6. Lymph node is infiltrated by monocytoid B cells surrounding germinal centers. This pattern is also referred to as "inverted follicular pattern." The monocytoid B cells have abundant; lightly staining cytoplasm and irregular nuclei. (H&E 40×, 400×).

SPLENIC MARGINAL ZONE LYMPHOMA, WITH OR WITHOUT VILLOUS LYMPHOCYTES

This is a proposed provisional entity in the new European-American classification of lymphoid neoplasms.[31] Most of the clinical and pathologic features were described in the past as splenic lymphoma with villous lymphocytes.[37,38] The mean age is over 60 years in most patients. Patients usually present with a markedly enlarged spleen and a low level of paraproteinemia. Most patients have circulating lymphocytes with villous cytoplasmic projections (figure 7). The diagnosis can be made by noting characteristic involvement of splenic white pulp. There is usually bone marrow and peripheral blood involvement without lymph node involvement. The clinical course is usually indolent, and splenectomy without chemotherapy may be curative in some patients.[38]

MANTLE CELL LYMPHOMA

This tumor represents most of the lymphomas classified as diffuse small cleaved (DSC) cell type in the WF.[36] Although rare cases of tumors originating from follicular center cells may be included, most DSC cell lymphomas take origin from cells normally found in the mantle zone surrounding germinal centers in lymph nodes.[31,36] The median age at presentation is in the late 50s to mid 60s. The survival of patients with mantle cell lymphoma is much shorter than the patients with other low-grade lymphomas.[39] Involved lymph nodes show diffuse to vaguely nodular infiltration by small to medium sized lymphoid cells, frequently with scattered uninvolved germinal centers (figure 8). Although most cases show irregular nuclei, there are some with rounder nuclei which could be difficult to differentiate from SLL/CLL. A diffuse small lymphoid infil-

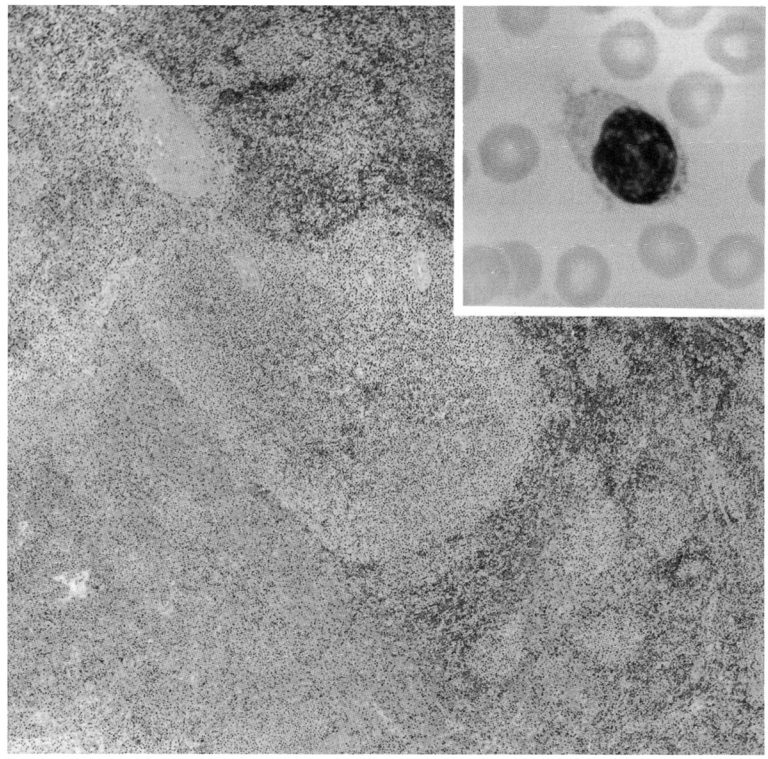

FIGURE 7. Spleen section shows marked white pulp infiltration by small lymphocytes, particularly with marginal zone expansion. The peripheral blood smear shows a circulating lymphocyte with villous projections. Unlike hairy cell leukemia the villous projections show polar distribution. (H&E 40×, WG 1000×).

trate without pseudoproliferation centers and paraimmunoblasts should raise a suspicion of mantle cell lymphoma.

The t(11;14)(q13;q32) translocation is characteristic of mantle cell lymphoma.[35,36] This translocation causes a cell cycle protein, cyclin D1, to be overexpressed in low-grade lymphomas.[40] The tumor cells are positive for B-cell markers CD19, CD20, and surface immunoglobulin, IgM and/or IgD types, and express CD5, but usually lack the CD23 antigen.[25] The intensity of CD20 and immunoglobulin light chain expression is usually higher than that of SLL/CLL.[26]

FOLLICULAR CENTER CELL LYMPHOMA

The prognosis of follicular lymphomas is worse in the elderly than in younger patients.[41] The neoplastic cells originate from the germinal centers of lymph nodes. Involved lymph nodes characteristically show a follicular pattern consisting of small cleaved and/or large noncleaved cells. The relative number of large cells determines the grade.[31] The tumor cells are usually CD5 negative. The presence of CD10 expression is useful in confirming the follicular center cell origin of this lymphoma; however, it is not present in all cases of follicular lymphomas.

The t(14;18)(q32;q21) chromosome translocation is reported to be present in 60 to 85 percent of cases.[42] This translocation causes overexpression of bcl-2 protein which prevents programmed cell death known as apoptosis.[43] Immunophenotypic demonstration of bcl-1 protein expression within follicles is helpful in differentiating follicular lymphoma from follicular hyperplasia.[44] However, this protein is also expressed in other low-grade lymphomas, and its expression cannot be used for differentiating from other types of lymphomas. The detection of bcl-2 translocation by polymerase

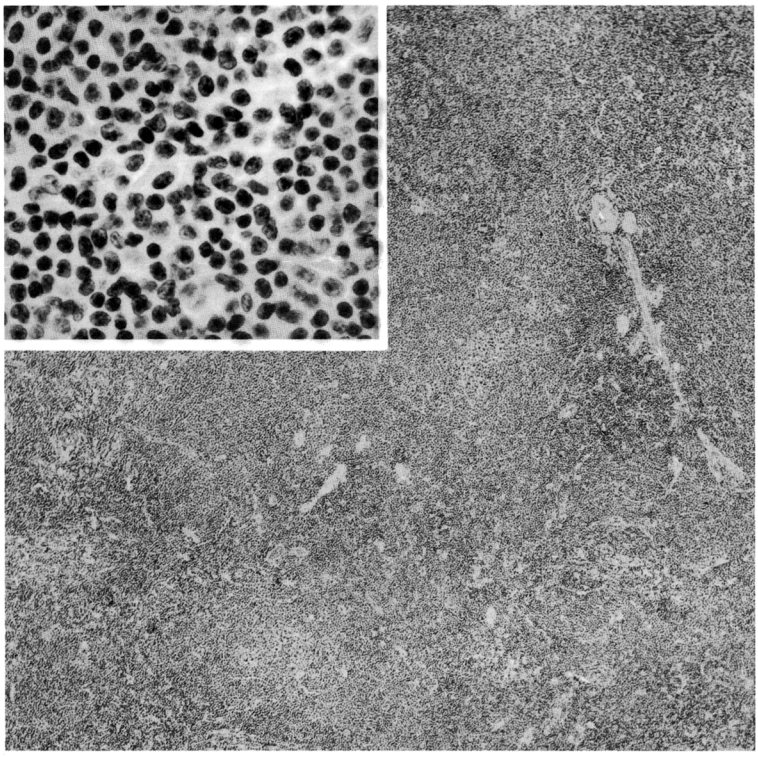

FIGURE 8. Mantle cell lymphoma. The lymph node shows a diffuse lymphocytic infiltrate, with occasional residual germinal centers. The lymphocytic infiltrate is composed of small cells with scant cytoplasm and slightly irregular, cleaved nuclei. (H&E 40×, 400×).

chain amplification allows extremely high sensitivity in detecting the presence of tumor cells.[45]

Conclusion

The low-grade lymphomas are in general diseases of the elderly, and outcome of therapy with current treatment modalities is frequently disappointing. The diagnosis of low-grade lymphomas usually requires a comprehensive analysis of the clinical, histologic, immunophenotypic, and genetic findings. The precise classification of these neoplasms is probably the first step in understanding their basic pathogenic mechanisms and designing a rational approach toward effective therapy.

Acknowledgment

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