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Intermediate Lymphocytic Lymphoma Encompassing Diffuse and Mantle Zone Pattern Variants

A Distinct Entity Among Low-Grade Lymphomas?

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Abstract—*Intermediate lymphocytic lymphoma has been operationally included among low-grade lymphomas, but few clinical data appeared to support definitely such an inclusion. The clinicopathologic features of* 13 *out of* 14 *cases of intermediate lymphocytic lymphoma either encompassing diffuse or mantle-zone pattern variants (ILL or MZL, respectively), diagnosed by conventional histology according to established criteria, are reported. Frozen section immunophenotypic analysis was also performed in* 10 *cases and enzyme studies were done in five. The* 14 *cases formed* 6.9% *of* 203 *non-Hodgkin's lymphomas (NHL) histologically diagnosed over a* 2*-year period. Among the* 13 *cases studied, there were nine males (five with ILL and four with MZL) and four females (one with ILL and three with MZL). Median age was* 59 *years. Splenomegaly* (46%), *high stage diseases* (100%), *involvement of bone marrow* (92%) *and peripheral blood* (38%), *and diffusion to and/or involvement of extranodal sites* (38%), *all were common findings at presentation.*

The 34 *low-grade NHL of the total series classified according to the Working Formulation did not significantly differ from the ILL/MZL group in terms of frequency of involvement of bone marrow* (69%) *and peripheral blood* (56%) *as well as diffusion to and/or involvement of extranodal sites* (26%). *In ILL/MZL, therapy modalities were not uniform and the short follow-up time precluded firm conclusions on prognosis. Immunohistology demonstrated that ILL/MZL diagnosed by adequate morphologic criteria is a fairly homogeneous entity, also sharing most of its consistent immunological features with low-grade NHL. Thus, ILL/MZL is a relatively frequent and consistently recognizable clinical and pathological entity that may deserve a distinct place among NHL according to the Working Formulation. Proper clinical studies are needed to establish on a firmer basis the prognosis and optimal treatment of ILL/MZL.*

INTRODUCTION

INTERMEDIATE lymphocytic lymphoma (ILL) [1] is a morphologically peculiar subtype among the non-Hodgkin's lymphomas (NHL) that shows cytologic features intermediate between those of malignant lymphoma of small lymphocytic type (well-differentiated lymphocytic lymphoma: WDLL) and small cleaved cell type (poorly differentiated lymphocytic lymphoma: PDLL) [2–4]. Histologically, ILL is characterized by a diffuse growth pattern, although vaguely nodular focal areas may be also found [1]. A nodular variant of ILL has been also described [5], termed 'mantle zone lymphoma' (MZL), in which atypical cells proliferate as wide mantles around non-neoplastic appearing germinal centers (mantle zone pattern).

Because of its distinctive morphologic [1] and immunophenotypic [1, 3, 4, 6, 7] features, ILL has been proposed [3,4] as a separate category of lymphocytic lymphoma in the international Working Formulation (WF) [8] and, similarly to MZL, it has been operationally included among low-grade NHL [9].

Relatively few clinical data [1, 4, 5, 10–12] have appeared in the literature so far which support definite inclusion of ILL/MZL among low-grade NHL. The scarcity of the above data also probably depends on the fact that ILL/MZL is seldom diagnosed as such, being arbitrarily placed by histopa-

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thologists into either WDLL or PDLL types because of the mixed nature of its neoplastic proliferation [2].

In the present study we report the clinicopathologic features of 13 morphologically and phenotypically homogeneous ILL/MZL cases observed in a single institution over a 2-year period.

MATERIALS AND METHODS

Two hundred and three cases of histologically proven NHL were evaluated between 1 May 1985 and 30 April 1987, at the Division of Pathology of the Centro di Riferimento Oncologico, Aviano. Cases with overt chronic lymphocytic leukemia (CLL) diagnosed by hematologic criteria only were excluded. Fourteen cases (6.9%) were classified as ILL (seven cases) or MZL (seven cases) on the basis of established histologic criteria [1, 5]. The other 173 cases could be placed in the WF categories [8] (156 in those from A to J and 17 in the miscellaneous category). The remaining 16 cases were described as unclassified (Table 1).

Clinical data were available in 13 ILL/MZL cases (six ILL and seven MZL). These cases formed the basis for the current study. Clinical data included age, sex, site and symptoms at presentation, staging according to Ann Arbor system [13], therapy modalities, response and survival. The response to therapy was classified as complete remission (CR), partial remission (PR) or no change. CR was defined as the total disappearance of all symptoms and clinically detectable disease. PR was defined as 50% or greater disappearance of all known tumor and the appearance of no new lesions. Survival time was measured from the time of first histologically proven diagnosis. When feasible, some of the above data were statistically compared with those of the 34 low-grade NHL included in the total series (Table 1) by using the χ-square test.

Histologic review data from conventionally stained sections of pretreatment lymph nodes and other involved tissues, bone marrow aspirates and peripheral blood smears were also available in the six ILL and seven MZL cases.

Immunophenotypic studies on frozen sections were done in five ILL and five MZL cases by using an avidin–biotin complex immunoperoxidase method [14] and selected antibodies as specified elsewhere [15, 16].

Enzyme analysis for adenosine triphosphatase (ATPase) and alkaline phosphatase was performed in two ILL and three MZL cases by using plastic-embedded tissue sections treated according to our previously published procedure [17].

RESULTS

The relevant data of the 13 patients with ILL/MZL are summarized in Tables 2 and 3.

There were nine males and four females (male to female ratio 2.2:1). Age ranged from 44 to 80 years (median, 59 years). In the low-grade NHL the male to female ratio was 1.1:1, with a median age of 63.5 years.

In the ILL/MZL group, two patients presented with B symptoms (weight loss, fever and night sweats). One patient presented with fatigue, dyspnea and abdominal distention due to prominent splenomegaly. One further patient presented with

Table 1. *Classification of* 203 *NHL cases according to major categories of the WF* [8] *and to criteria established for ILL* [1] *and MZL* [3] (*2-year period*)

WF major categories	No. of cases	Percentage
Low grade (34 *cases*)		
A. Small lymphocytic	16	7.9%
B. Follicular predominantly small cleaved cell	8	3.9%
C. Follicular mixed, small cleaved and large cell	10	4.9%
Intermediate-grade (75 *cases*)		
D. Follicular predominantly large cell	10	4.9%
E. Diffuse small cleaved cell	3	1.5%
F. Diffuse mixed, small and large cell	38	18.7%
G. Diffuse large cell	24	11.8%
High grade (47 *cases*)		
H. Large cell, immunoblastic	35	17.2%
I. Lymphoblastic	7	3.4%
J. Small noncleaved cell	5	2.5%
Miscellaneous	17	8.3%
Unclassifiable	16	7.9%
ILL/MZL	14	6.9%
Total cases	203	100%

NHL, Non-Hodgkin's lymphomas; WF, Working Formulation; ILL, intermediate lymphocytic lymphoma; MZL, mantle zone lymphoma.

Table 2. Clinicopathologic features of 13 patients with ILL and MZL

Cases	Age	Sex	Sites of involvement LY	S	H	BM	PB	OES	Stage	Therapy	Response	Follow-up (months)
ILL	60	M	+	p+*	p+	p+	+	L+; pW+	IVA	BEPP/CHOP	PR	34 A
ILL	79	M	+	+	NE	p+	+	–	IVA	Idarubicin§	PR	10 D
ILL	44	M	+	+	–	p+	+	–	IVB	BEPP/CHOP	PR	22 A
ILL	46	M	+	–	–	p+	+	–	IVA	CHOP	CR	20 A
ILL	80	F	+	–	–	p+	+	pST+	IVA	Idarubicin§	NC	11 D
ILL	44	M	+	–	–	p+	–	pW+	IVA	CHVmPOB	PR	13 A
MZL	49	M	+	+	+	p+	–/+	–	IVB	COP/BAP	NC	23 D
MZL	59	M	+	+	–	p+	–	pST+	IVA	BEPP/CHOP	PR	26 A
MZL	60	M	+	p+	+(p–)	p+	–	–	IVA	COP-BEPP/CHOP	CR	45 A
MZL	52	F	+	+	–	p+	+	pBR+	IVA	BEPP/CHOP	PR	21 A
MZL	67	F	+	–	–	p–	–	–	IIIA	ProMACE MOPP	CR	19 A
MZL	59	F	+	–	–	p+	–	–	IVA	ProMACE MOPP	CR	16 A
MZL	66	M	+	–	–	p+	–/+	–	IVA	Total body irradiation	CR	16 A

ILL, Intermediate lymphocytic lymphoma; MZL, mantle zone lymphoma; LY, lymph nodes; S, spleen; H, liver; BM, bone marrow; PB, peripheral blood; OES, other extranodal sites; p, pathological stage; L, lung; W, Waldeyer's ring; NE, not evaluable because of liver cirrhosis; *, at restaging workup; ST, stomach; BR, breast; –/+, peripheral blood positive in the course of the disease; BEPP, bleomycin, etoposide, procarbazine, prednimustine; CHOP, cytoxan, adriamycin, oncovin, prednisone; CHVmBOP, cytoxan, adriamycin, teniposide, prednisone, oncovin, bleomycin; COP, cytoxan, oncovin, prednisone; BAP, bleomycin, adriamycin, prednisone; ProMACE MOPP, methotrexate, adriamycin, cytoxan, etoposide, mechloretamine, oncovin, procarbazine, prednisone; PR, partial response; CR, complete response; NC, no change; A, alive; D, dead; §, 4-demetoxydaunorubicin.

Table 3. Comparison of some clinical features of patients with ILL and MZL reported in the major series from the literature [1, 4, 5, 10]

Features	42 ILL [1]	12 MZL [5]	19 ILL [10]	12 ILL [4]	Present series of cases Six ILL	Seven MZL
M/F ratio	5:1	2:1	1:5	1:1	5:1	1.3:1
Median age (years)	65	56.5	61	60	53	59
Presenting with splenomegaly	38%	83%	100%	75%	50%	42%
Presenting with hepatomegaly	24%	33%	10%	41%	16%	28%
Bone marrow involvement	28/37 (76%)	66%	93%	9/11 (81%)	100%	85%
Peripheral blood involved	21%	None	21%	41%	83%	14%
High stage (III and IV)	95%	83%	100%	100%	100%	100%
Overall median survival	31 mo	41 mo	30 mo	36 mo	*	*

ILL, Intermediate lymphocytic lymphoma; MZL, mantle zone lymphoma; *, data not available because of short follow-up.

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dyspnea due to lung involvement by lymphoma and two other patients complained of epigastric pain due to gastrointestinal involvement. All of the 13 patients had multiple (11 cases) or single (two cases) peripheral lymph node enlargement; the lymphangiogram was positive in all of the four patients examined. Other sites of involvement at presentation included breast (one patient) and Waldeyer's ring (two cases). Six patients presented with splenomegaly, this being massive in two. Hepatomegaly, evaluable in three cases (Table 2), was recorded in four patients. Peritoneoscopy was performed in two cases and biopsies demonstrated liver and spleen involvement in one patient at staging and re-staging workup, respectively, while spleen involvement was documented at staging in the other. Bone marrow biopsy was performed in all patients, being positive in 12. Five patients had peripheral blood involvement at presentation while two others developed it in the course of the disease. Monoclonal serum protein, IgM type, was found in one patient only. All the 13 patients had high stage (III or IV), as did most (80.6%) of those with low-grade NHL.

Ten patients were treated with combination chemotherapy (Table 2); four of them had CR, five had PR and one did not show change. Two elderly patients were treated with single agent chemotherapy; one underwent PR and the other showed no change. The remaining patient was treated with total body irradiation and a CR was observed.

As of May 1988, three patients deceased 10 months, 11 months and 23 months after diagnosis, respectively.

Pathologic features

Lymph nodes. At low-power, eight cases (four ILL and four MZL) showed a complete effacement of the nodal architecture; partial effacement was documented in the remaining five. Capsule and adjacent tissues were infiltrated in two ILL and three MZL cases. In most instances, lymph sinuses were compressed in MZL and obliterated in ILL.

In MZL, the tumor cells formed wide mantles surrounding residual germinal centers of variable size (mantle zone pattern) (Figs. 1 and 2) or were composed of nodular aggregates lacking such centers (nodular pattern, seen in one case) or grew with a diffuse fashion. Combination of all of these three growth fashions was seen in two cases whereas in the remaining four dual combination were seen, that is mantle zone plus diffuse (two cases) or plus nodular (one case), or nodular plus diffuse (one case).

In ILL, the tumor cells showed a diffuse pattern of growth in one case while in the other five vaguely nodular areas were also present.

Proliferation centers analogous with those of WDLL/CLL were found in three ILL cases.

Cytologically, the predominant neoplastic population in both MZL and ILL was composed of small lymphoid cells with slightly irregular or indented nuclear contours (intermediate cells) (Fig. 3). In a second lymph node biopsy specimen from a MZL case, however, as we reported elsewhere [18], the nuclei were cerebriform. In both MZL and ILL cases, a lymphoid cell population either having entirely round nuclei or angular and cleaved nuclei could be detected amidst the tumor proliferation (Fig. 4). Plasma cells and plasmocytoid cells were not increased in any case. Mitotic rate was low in most cases.

Other tissues. In the 12 positive bone marrow biopsies, the infiltration pattern was nodular in five cases (three ILL and two MZL), diffuse in three (two ILL and one MZL), interstitial in one ILL case and microfocal in a further MZL case. In two MZL cases the pattern was not evaluated. Cytologically, the majority of infiltrating tumor cells had the same intermediate features as those seen in lymph nodes.

In the seven positive peripheral blood smears, the usual picture consisted of abnormal small- to medium-sized lymphoid cells with irregular nuclear outlines, with only rare cells featuring cleaved or rounded nuclei (Fig. 5).

In the positive spleen and liver biopsies, atypical lymphoid cells with intermediate morphology infiltrated the white pulp or portal tracts (Fig. 6), respectively. Other sites of extranodal involvement included breast (Fig. 7), duodenum and stomach (Fig. 8) and Waldeyer's ring.

No statistically significant difference was found between the group of ILL/MZL cases and the low-grade NHL of our total series, respectively, in terms of frequency of bone marrow involvement (92% vs. 69%), frequency of peripheral blood involvement (54% vs. 56%), as well as frequency of involvement of and/or diffusion to extranodal sites (38% vs. 26%).

Special studies

The results of immunophenotypic studies performed in ILL and MZL cases of the present series have been reported elsewhere [15, 16, 18] and only a brief summary is given here (see also Table 4). The B-cell nature of lymphoma cells was demonstrated in all of the 10 cases tested. Also, cells expressed surface IgD and IgM, with either kappa or lambda chain restriction. In all but one case, the cells clearly expressed the mantle zone-B-cell related [19] antigen Leu-8 and consistently showed immunoreactivity for the T-cell related [20] antigen Leu-1. Reactivity for common acute lymphoblastic leukemia antigen (CALLA) and B-cell related [20] antigen BA-2 was absent in all cases.

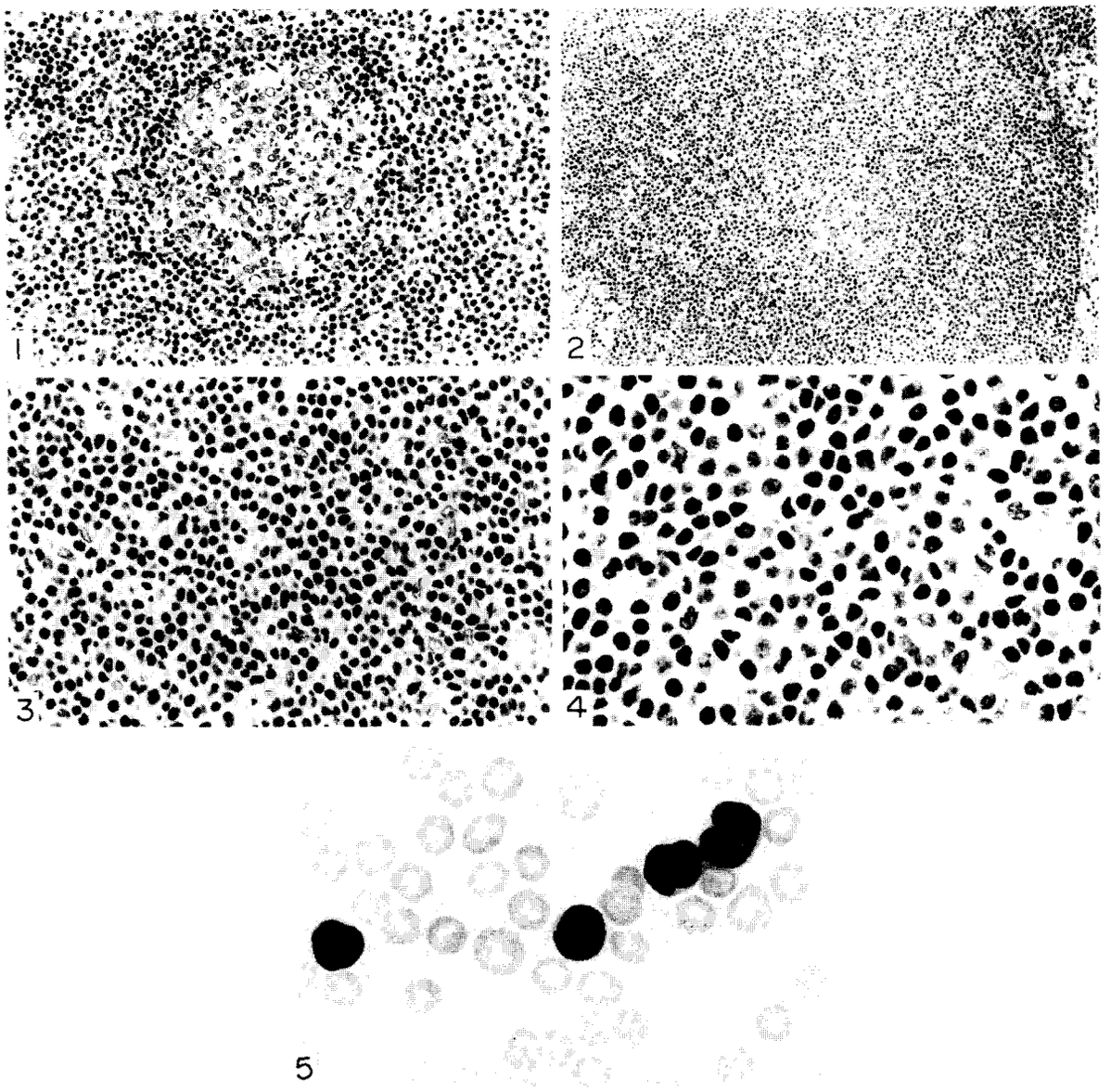

Fig. 1. *Lymph node from a patient with MZL. A proliferation of atypical small lymphoid cells surrounds a residual germinal center (mantle zone pattern) (H & E, × 35 original magnification).*

Fig. 2. *Lymph node from a patient with MZL. A proliferation of atypical small lymphoid cells nearly obliterates a residual germinal center (mantle zone pattern) (H & E, × 22 original magnification).*

Fig. 3. *Lymph node from a patient with ILL. There is a proliferation of atypical small- and medium-sized lymphoid cells with irregular nuclear outline that have intermediate features between small round lymphocytes and small cleaved cells (H & E, × 35 original magnification)*

Fig. 4. *Lymph node from a patient with ILL. Detail of prevailing tumor cells shows that these have irregular nuclear outline and condensed chromatin pattern. A few cells with either round nuclei and small nucleoli (prolymphocytes) or more angular and cleaved nuclear contour also are present (H & E, × 87 original magnification).*

Fig. 5. *Peripheral blood smear from a patient with MZL. Atypical small- and medium-sized lymphoid cells feature a morphology spectrum of nuclear abnormalities ranging from an almost entirely round contour to a 'buttock-like' shape (Giemsa, × 87 original magnification).*

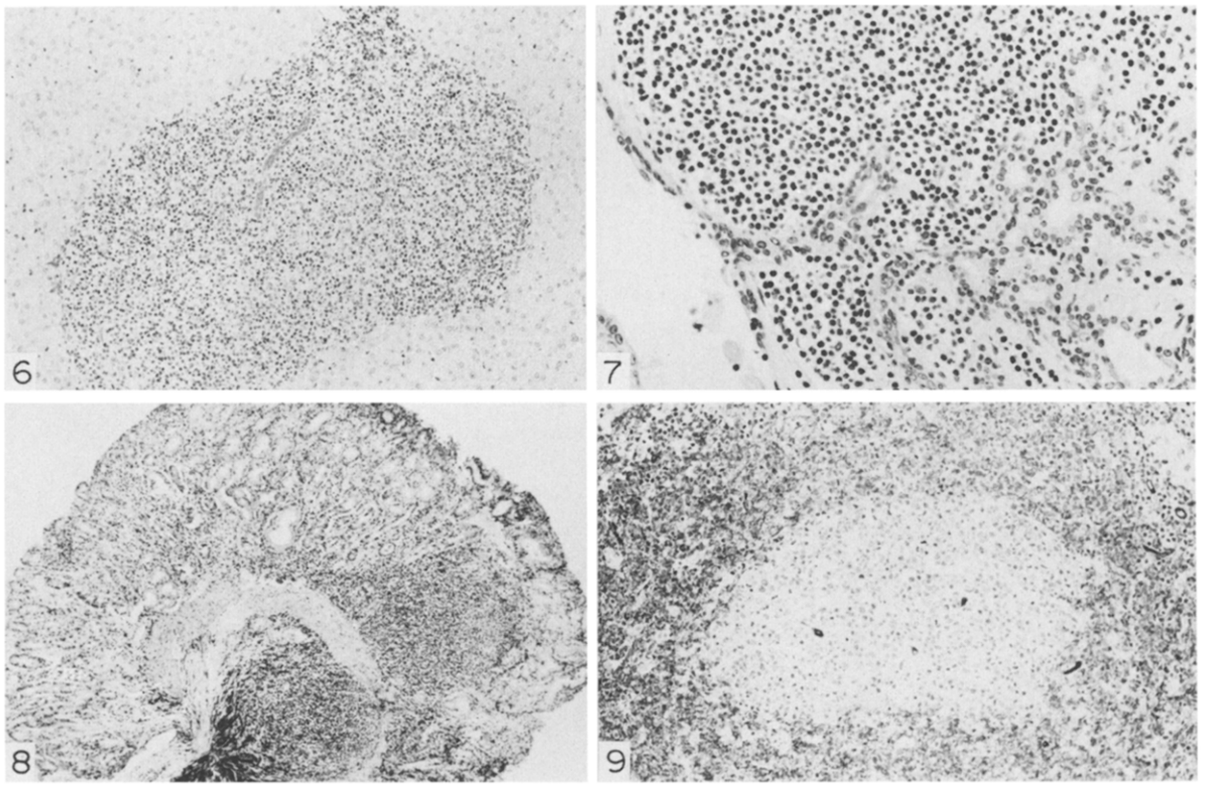

Fig. 6. Liver biopsy from a patient with ILL. Atypical small- to medium-sized lymphoid cells fill a portal tract (H & E, × 22 original magnification).

Fig. 7. Breast biopsy from a patient with MZL. Atypical small lymphoid cells infiltrate and replace glandular structures (H & E, × 22 original magnification).

Fig. 8. Gastric biopsy from a patient with MZL. Focal infiltration of tumor cells arranged in a nodular fashion is demonstrated within mucosal and submucosal layers (H & E, × 9 original magnification).

Fig. 9. Lymph node from a patient with MZL. Tumor cells surounding a residual germinal center (mantle zone pattern) are positive for alkaline phosphatase reaction. This enzyme activity is demonstrable also in small vessels (plastic-embedded section, × 22 original magnification).

Table 4. Antibody and enzyme panel used and results of the immunophenotypic and enzyme in situ *studies*

Immunophenotypic study Antibody (to)	MZL group*	ILL group*
kappa/lambda restriction	5/5	5/5
sIgD	5/5	5/5
sIgM	5/5	5/5
Leu 8	4/5	5/5
Leu 1	4/5	5/5
Leu 14	5/5	5/5
Leu 4	0/5	0/5
CALLA	0/5	0/5
BA-2	0/5	0/5
Enzyme study Enzyme	MZL group*	ILL group*
Adenosine triphosphatase	3/3	0/2
Alkaline phosphatase	3/3	0/2

*No. of cases positive/No. of cases tested.

Enzyme studies showed that ATPase and alkaline phosphatase activities were present in the tumor cells in all three MZL (Fig. 9) but absent in two ILL cases tested (see Table 4).

DISCUSSION

ILL/MZL is a recently described [1, 5, 21] entity that is seldom diagnosed as such because of the mixed nature of its neoplastic cells (intermediate cells), that show cytologic features between those of WDLL and PDLL. Thus, it seems difficult to yield data on the 'true' frequency of ILL/MZL. We found that 6.9% of 203 NHL seen over a 2-year period can be placed in the ILL/MZL category when, as suggested [4], established histologic criteria [1, 5] are adopted. The above frequency (6.9%) is strictly similar to that found for ILL (8.4%) in the Nebraska Lymphoma Registry by Weisenburger *et al.* [4]. Moreover, ILL represented 6.4% of the cases upon a review [1] of 770 original cases of diffuse WDLL and PDLL. These data appear to strongly suggest that ILL/MZL has a not negligible frequency among NHL.

ILL/MZL is not mentioned in the NHL categories of the original WF [8]. Omission of this lymphoma from the WF is unfortunate in light of the widespread use of the WF in international studies. Recently, Jaffe *et al.* [22] have stated that clinically, morphologically and immunophenotypically ILL/MZL appear identical to centrocytic lymphoma of the Kiel Classification; thus, if ILL/MZL had to be assigned to a category in the WF, most would be classified as malignant lymphoma, diffuse, small cleaved cell type, a category closely related to malignant lymphoma, centrocytic type, in the Kiel Classification [22]. Moreover, it has been reported that diffuse small cleaved cell lymphoma immunologically appears to be more closely related to small lymphocytic lymphoma (WDLL) and ILL than to follicular small cleaved cell lymphoma [23]. Although ILL was reported to have a clinical behavior similar to diffuse PDLL [1] (that is, to an intermediate grade of malignancy according to the WF scheme), recently it has been proposed [3, 4] as a separate category of lymphocytic lymphoma in the WF. Moreover, both ILL and MZL have been included among low-grade NHL in a revised operational scheme [9] of the WF. As conventional inclusion of ILL/MZL in either low-grade or intermediate-grade NHL may bear therapy implications (that is, potential risk of under- or over-treatment), it seems necessary to perform adequate clinical studies on large series of patients with ILL/MZL diagnosed by strict adherence to established histologic criteria [1, 5].

When these criteria are applied, however, a fairly consistent clinical picture of ILL/MZL emerges (Table 3). This is also in keeping with that reported by other authors [7, 11, 12, 24]. Usually, patients are middle-aged or older males presenting with splenomegaly and advanced stage disease. In spite of the latter, however, the clinical course is relatively indolent, especially in MZL [4, 5, 12]. Extranodal occurence, particularly in the gastrointestinal tract [11] or rare sites such as the central nervous system [25] and thyroid [26], has been reported.

As we could confirm by the current study, several of the clinicopathologic features of the ILL/MZL are similar to those commonly found in low-grade NHL. These features include age group, advanced stage disease, and high frequency of bone marrow and peripheral blood involvement. Moreover, we did not find any significant difference between ILL/MZL and low-grade NHL also in terms of involvement of and/or diffusion to extranodal sites. Prominent splenomegaly without high lymphocyte blood counts and absence of monoclonal gammopathy, as observed in our cases, seem to be more typical for ILL/MZL than for WDLL, however [4].

Unfortunately, we could not make a definite comparison between survival data of our low-grade NHL and ILL/MZL because of the short follow-up time of the latter group. Also, the heterogeneous therapy regimens employed in the ILL/MZL cases of our series (Table 2) do not allow us to suggest what the optimal treatment for these patients would be. Specifically devised clinical studies are clearly necessary to this end.

The architectural and cytological appearance of ILL and MZL in the lymph nodes and other tissues found in the current study were entirely consistent with those reported in the papers [1, 5] describing

the morphologic criteria for diagnosing these entities.

ILL/MZL diagnosed by these criteria appears to be a fairly homogeneous entity also in terms of the immunophenotypic features of proliferating cells [15, 16]. These features (positivity for surface IgD and IgM, Leu-1, and Leu-8; negativity for CALLA and BA-2) are entirely consistent with those reported in other studies from the literature [3, 4, 7, 27–29]. The most recent of these studies [3, 4, 7] also suggest a close relationship between ILL/MZL and WDLL/CLL. Besides some confirmatory cytogenetic common abnormalities [4], a further piece of evidence of such a relationship is offered by shared immunoreactivity for Leu-1 and Leu-8 antigens [15, 16]. The Leu-8 antigen is also expressed by the circulating cells of B-CLL [30] as well as by normal mantle zone B-cells [19].

The latter finding also raises the still unresolved problem of the cell origin of ILL/MZL, thought to arise from the primary follicle and/or mantle zone of secondary follicle [2, 5, 24]. Such an origin had been first postulated on the basis of the frequent (about 50% of the cases) positivity for the alkaline phosphatase [21, 31], this suggestion being later confirmed both by immunophenotypic [3, 28, 32] and enzyme [27, 28] studies. In our tested cases, ATPase and alkaline phosphatase were detected in MZL only. Studies are necessary to compare the presence of these enzyme activities with the immunophenotype of ILL/MZL cells.

In conclusion, taking into account all of the above data from clinical, morphologic, immunophenotypic, cytogenetic, and enzyme histochemistry studies—irrespective of the still debated cell origin—ILL/MZL appears to be a relatively frequent and consistently recognizable clinical and pathologic entity which may deserve a distinct place among NHL. Proper clinical studies are needed to establish on a firmer basis its prognosis and optimal treatment.

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