Primary Malignant Lymphomas of the Spleen

A Morphologic and Immunohistochemical Analysis of 17 Cases

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Seventeen cases of primary malignant lymphoma of the spleen (PMLS) were identified among 500 splenectomy specimens showing involvement by Hodgkin's disease or non-Hodgkin's lymphoma. All PMLS represented non-Hodgkin's lymphoma and most of them were of B-cell origin. In two cases PMLS were associated with hamartomas of the spleen (splenomas). Histologic and immunohistochemical studies did not reveal any differences between PMLS and disseminated malignant lymphomas with splenic involvement with regard to morphologic features, immunophenotype, host cell infiltrates, or proliferation activity. The reasons for the infrequent occurrence of primary lymphomas in the spleen may not be sought in a special immunophenotype of PMLS, a vigorous host response in the spleen, or in a lower proliferation activity of splenic lymphomas.
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ALTHOUGH SPLENIC INVOLVEMENT in both disseminated Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) is commonly encountered[1–3] primary, *i.e., de novo* splenic HD or NHL for unknown reasons are only rarely diagnosed.[4–6] Although cases of "primary" malignant lymphomas of the spleen (PMLS) have been repeatedly reported, close scrutiny of these cases reveals that in most instances the malignant lymphoma (ML) is not only present in the spleen and in splenic hilar lymph nodes, but that extraabdominal lymph nodes, and frequently the bone marrow also, harbor extensive neoplastic infiltrates. In these cases the ML in question clearly has been designated as a PMLS because the tumor burden was predominantly localized in the spleen. This reflects the ambiguity of the term "primary splenic lymphoma."

In the current study we identified ML which, according to stringent diagnostic criteria, had developed primarily in the spleen and to study some of the possible reasons for the infrequent occurrence of these lesions. Specifically, we analyzed the clinical presentation, the immunophenotype and host cell infiltrates, and in the cases with frozen tissue available, the proliferation activity of the ML, since one could hypothesize that (1) PMLS are infrequently diagnosed because they do not cause symptoms until dissemination which obscures the primary localization in the spleen has occurred; (2) the spleen's microenvironment which contains a multitude of potentially tumoricidal cells of the mononuclear phagocyte system would be hostile to nascent neoplastic cells[7,8] which may be reflected by larger numbers of immunocompetent cells and a lower proliferation activity than in disseminated ML; and (3) the remote possibility that PMLS possess a distinct immunophenotype pointing to an origin from lymphatic cells predominantly present in the spleen.

Materials and Methods

As part of a larger study of morphologic manifestations of ML in the spleen[9] our routine and consultation files were reviewed for cases of possible PMLS. To qualify as a case of PMLS the following requirements had to be met in each case: (1) there had to be an adequate clinical history; (2) in addition to the splenectomy specimen there had at least one lymph node specimen, and a liver and a

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bone marrow biopsy specimen obtained at the time of splenectomy or shortly thereafter had to be available for review; and (3) the main tumor burden was present in the spleen, splenic hilar lymph nodes but no other lymph nodes were involved, and there was no or minimal lymphomatous infiltration of liver and bone marrow or any other organs. All cases were classified according to the updated Kiel classification of malignant lymphomas.[10]

In each case culled from our files the macroscopic findings, especially splenic weight, as well as number and size of infiltrates were recorded. Other pertinent findings, especially the results of immunophenotyping in frozen sections, were also obtained. Paraffin blocks were recut and stained with hematoxylin-eosin, Giemsa, periodic acid-Schiff (PAS), and Gomori's silver stain. Serial sections from the same blocks were subjected to an immunohistochemical study with a panel of monoclonal antibodies (Table 1) using a modified immunoalkaline phosphatase method.[11] This panel was selected in order to yield information about the immunophenotype of the neoplastic cells as far as may be ascertained in formalin-fixed and paraffin-embedded tissue, about the contents of tumor-associated immunocompetent accessory and effector cells, and in some cases with fresh tissue available, about the proliferation activity of the neoplastic cells.

TABLE 1. Antibodies Used in the Current Study

Antibody	Specificity	Source
Immunophenotyping of malignant lymphomas		
UCHL1*	CD45RO T-cells	Dako
MT1	T-cells, some B-cells	Biotest
MT2	T-cells, some B-cells	Biotest
MB1	B-cells	Biotest
MB2	B-cells	Biotest
L26*	CD20 B-cells	Dako
KiB3	B-cells	Prof. M. R. Parwaresch
LN1	CDw75 B-cells	Biotest
LN2	CD74 B-cells (HLA-DR)	Biotest
BerH2	CD30 Ki1 antigen	Prof. H. Stein
LeuM1*	CD15 Granulocytes	Becton Dickinson
Ki 67	Proliferating cells	Dako
Identification of host cell infiltrates		
BerMacDRC CD35	Dendritic reticulum cells	Prof. H. Stein
S-100	T-accessory cells	Dako
KP1/EBM11 CD68	Macrophages	Prof. D. Y. Mason
Identification of splenic structures		
Collagen IV	Basal membranes	Dianova
Vimentin	Sinus lining cells	Dako
FVIIIag	Endothelium	Dako

Becton-Dickinson: Becton-Dickinson, Heidelberg; Biotest: Biotest AG, Dreieich; Camon: Camon GmbH, Wiesbaden; Dako: Dakopatts, Hamburg; Dianova: Dianova GmbH, Berlin, FRG.

* Also used for identification of host cell infiltrates.

The results and relevant information, *e.g.*, frozen tissue immunophenotype, obtained at the time of the initial diagnosis, were compared with the splenic findings in ten randomly selected cases of disseminated ML for each entity as defined by the Kiel classification. Except for the immunophenotyping the number of the reactive cells was assessed by a semiquantitative scoring system (0, +, ++, +++). Preliminary studies had indicated a close correlation between these semiquantitative results and a quantitative determination. Statistical significance was tested by the u test. Follow-up was available for 14 patients (7 months to 12 years; mean, 42 months).

Results

General Findings

Among the 500 cases of splenectomy specimens with ML received between 1969 and 1989 (162 cases of HD and 338 NHL), 17 cases were identified which fulfilled the above-mentioned criteria and which were diagnosed as PMLS. Primary splenic HD could not be identified, and all but three cases were NHL of B-cell origin (Table 2). In 14 cases exploratory laparotomy and splenectomy were performed because of splenomegaly of unknown origin; in six of these patients nodular lesions splenic lesions were evident in either ultrasound or computed tomography (CT) studies. Four of these patients underwent splenectomy because of unexplained thrombocytopenia in addition to splenomegaly without evidence of nodular splenic lesions. Three additional patients required surgical exploration because of fever, nonspecific malaise, and weight loss with associated splenomegaly. In all three patients the B symptoms promptly subsided after splenectomy as did the thrombocytopenia. Four patients received adjuvant cytotoxic polychemotherapy.

Follow-up data from 14 patients reveal that seven patients died from disseminated disease (four lymphoplasmacytoid, one centroblastic-centrocytic [CB-CC], and two immunoblastic lymphomas), whereas one patient died of unrelated causes (pleomorphic T-cell lymphoma, medium cell type). Three patients (two lymphoplasmacytoid and one pleomorphic T-cell lymphoma, large cell type) are alive with disease, whereas three patients (two centroblastic-centrocytic and one centroblastic lymphoma) are alive without evidence of disease 22, 36, and 68 months, respectively, after splenectomy.

Morphologic Findings

On gross examination, PMLS did not differ from their disseminated counterparts, *i.e.*, lymphoplasmacytoid and centroblastic-centrocytic NHL caused moderate to marked splenomegaly and multiple, sometimes confluent nodular lesions in the splenic parenchyma which were

TABLE 2. Primary Non-Hodgkin's Lymphomas of the Spleen According to the Updated Kiel and the Working Classification of Malignant Lymphomas

	No.
Lymphoplasmacytoid NHL/small lymphocytic, plasmacytoid ML	7
Plasmocytoid NHL/plasmacytoma	1
Centroblastic-centrocytic NHL/follicular, mixed small and large cell ML	3
Centroblastic NHL/diffuse, large noncleaved cell ML	1
Immunoblastic NHL/large cell, immunoblastic ML	2
Peripheral T-cell lymphomas	
T zone lymphoma	1
Pleomorphic, medium cell type	1
Pleomorphic, large cell type	1

NHL: non-Hodgkin's lymphoma; ML: malignant lymphoma.

more distinct in CB-CC. The sole plasmacytoid ML showed splenomegaly (700 g) and a gray–white cut surface which was mostly homogenous but also exhibited small nodular densities. This was also the case in one of the peripheral T-cell lymphomas of the pleomorphic medium cell type, whereas a pleomorphic T-cell lymphoma of the large cell type exhibited nodular lesions. This also was true for high-grade malignant lymphomas which were usually associated with tumor nodules up to 6 cm in diameter (Fig. 1). One immunoblastic lymphoma showed a partly nodular, partly diffuse infiltration of the splenic parenchyma. Surprisingly, one centroblastic and one T-zone lymphoma were associated with several well-circumscribed dark nodular lesions of up to 6 cm in diameter which turned out to be splenic hamartomas (Fig. 2).

Histologically, PMLS were indistinguishable from disseminated tumors with regard to their cytologic composition and their infiltration pattern in the spleen. Briefly, the majority of the lymphoplasmacytoid ML showed a nodular infiltration pattern with predominant white pulp involvement and pulp cord invasion at the periphery of the lesion; in addition, in two cases a mantle zone type infiltrate was present. Centroblastic-centrocytic lymphomas caused nodular infiltrates usually located in the vicinity of an erstwhile splenic follicle and consisting mainly of centroblasts and centrocytes with an associated infiltrate of smaller centrocyte-like cells (the so-called follicular and diffuse type of the Kiel classification). All of the high-grade lymphomas were composed of randomly distributed nodular infiltrates with sheet-like proliferations of neoplastic cells broadly invading splenic parenchyma. In contrast, the low-grade peripheral T-cell lymphoma presented with an organoid appearance, *i.e.*, mature-appearing neoplastic T-cells extended from the T-cell domains in the periarteriolar lymphoid sheaths into the surrounding tissue. In none of the cases with associated splenic hamartoma neoplastic cells could be detected within the hamartoma.

Immunohistochemical Results

Immunophenotyping in both frozen and paraffin sections did not reveal appreciable differences between PMLS and disseminated malignant lymphomas. The results were in keeping with previously published analyses of ML with monoclonal antibodies.[12–16] The only remarkable case in our series proved to be the extramedullary plasmacytoma of the spleen which was negative for all antibodies used except for the CD30 (BerH2)-antibody. The same applies to the number and the arrangement of accessory cells within the neoplastic infiltrates. Dendritic reticulum cells

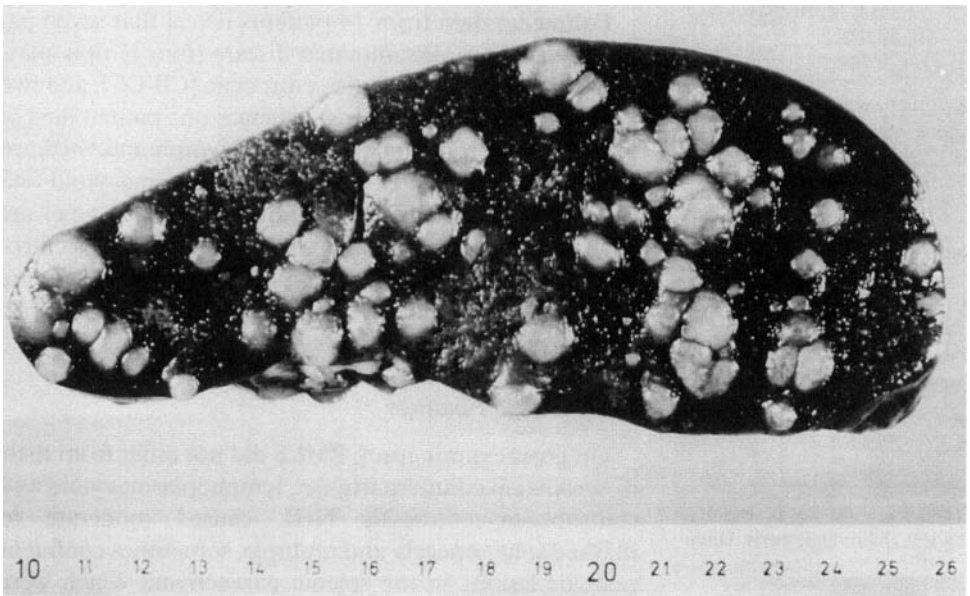

FIG. 1. Macroscopic appearance of a primary centroblastic lymphoma of the spleen. Notice the dissemination throughout the splenic parenchyma; in contrast, splenic hilar lymph nodes did not contain ML.

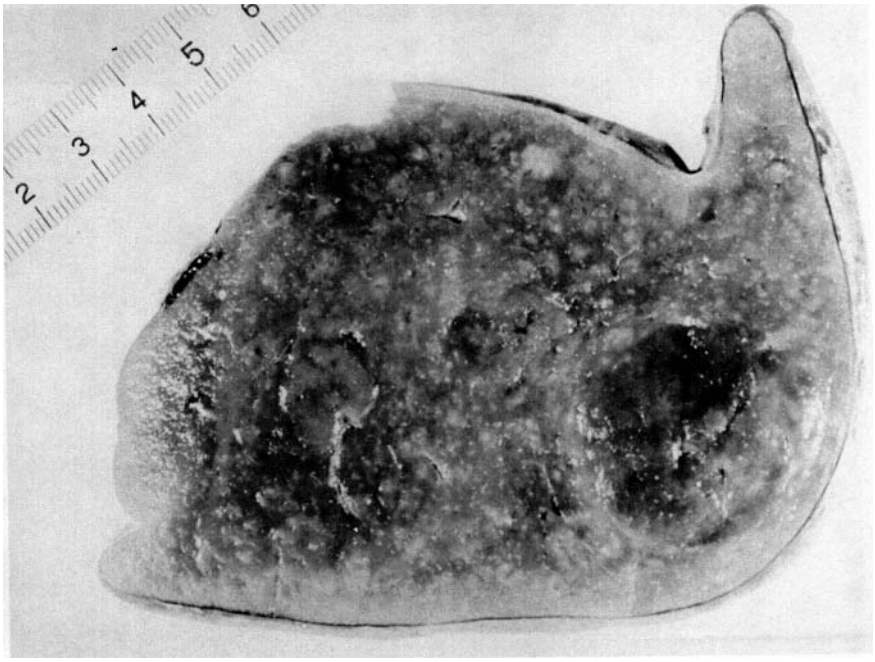

FIG. 2. Peripheral T-cell lymphoma of the spleen with associated splenic hamartomas, which are visible as prominent darker nodular lesions.

were present as vaguely nodular irregular meshwork in all cases of lymphoplasmacytoid ML, whereas the CB-CC cases were characterized by relatively dense nodular networks within the central ("follicular") portions of the infiltrate (Fig. 3).

Dendritic reticulum cells were absent from aggregates of neoplastic T-cells and were observed only very infrequently within centroblastic or immunoblastic lymphoma. These findings were also obtained in disseminated ML. S-100-positive T-accessory cells were found both within the neoplastic tissue (especially in T-cell lymphomas) and at the periphery of the lesions in B-cell lymphoma. A band-like arrangement was most conspicuous in the CB-CC cases where S-100+ cells (Fig. 4) were intermingled with CD45RO+ CD4+ T-cells at the periphery of the follicular lesions (Fig. 5). Again, there was no dis-

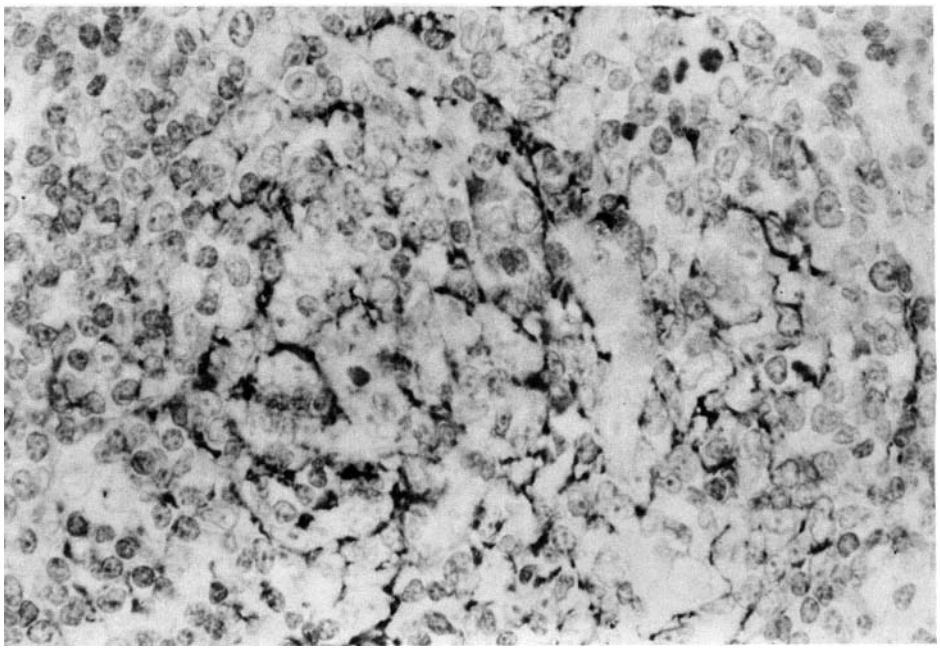

FIG. 3. Network of dendritic reticulum cells within a follicular infiltrate of a primary splenic CB-CC (Ber-MacDRC, APAAP, H, ×360).

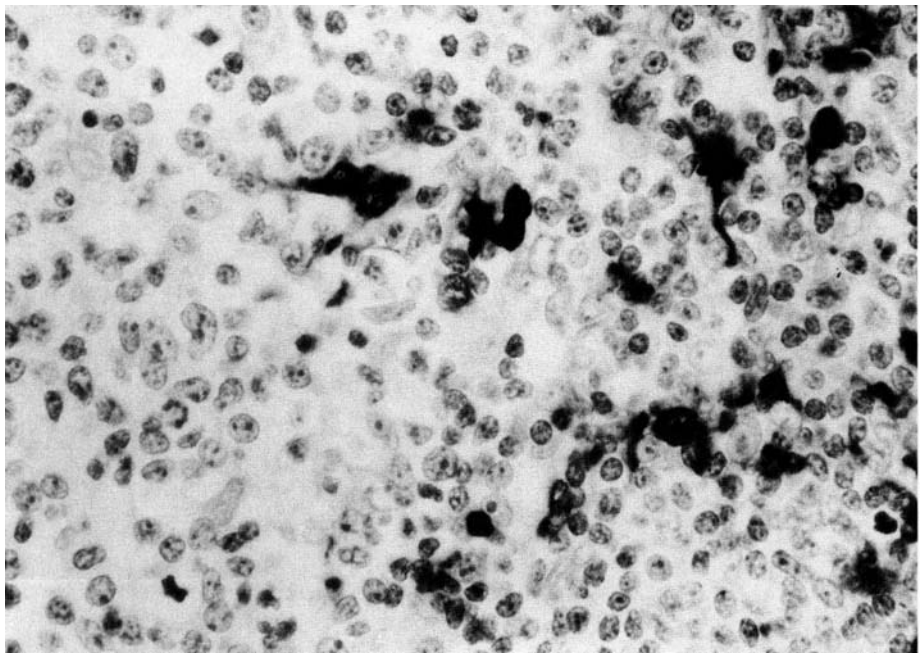

FIG. 4. S-100-positive T-accessory cells (mostly interdigitating reticulum cells) at the periphery of a splenic centroblastic lymphoma (APAAP, H, ×360).

cernible difference with regard to spatial distribution and number when compared with disseminated ML. Although CD45RO+ T-lymphocytes and CD68+ macrophages, present both within the infiltrates (*e.g.*, in lymphoplasmacytoid or in centroblastic and immunoblastic ML) and at their periphery (*e.g.*, CB-CC) were encountered in rather variable amounts, high-grade ML and T-cell lymphomas tended to contain more macrophages. It has to be noticed, however, that the number of macrophages and their phagocytic activity in the nonneoplastic splenic parenchyma closely correlated with the presence of hypersplenism which morphologically was represented by hemophagocytosis, siderosis, and foam cells. In contrast, the number of reactive T-lymphocytes was highest in the immediate vicinity of follicular infiltrates of CB-CC. Again, no significant difference could be demonstrated between

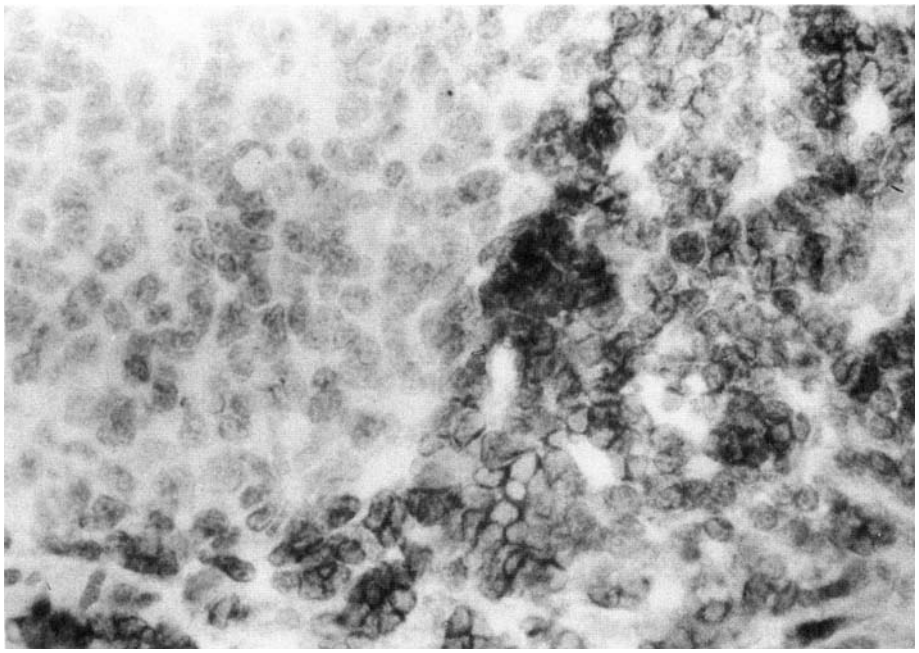

FIG. 5. Band-like arrangement of numerous CD4-positive T-cells around a follicular infiltrate of a splenic CB-CC (Leu3ab, APAAP, H, ×360).

PMLS and disseminated disease. This also holds true for the proliferation activity which had been determined in eight cases (three lymphoplasmacytoid, two centroblastic-centrocytic, and one centroblastic as well as a T-zone and a pleomorphic T-cell lymphoma). Highest numbers of Ki67+ neoplastic cells were visible in the pleomorphic T-cell lymphoma of the large cell type, in centroblastic, and in the CB-CC ML. A statistically significant difference from controls could not be ascertained.

Discussion

The subject of PMLS has long been a controversial issue,[17,18] since the difficulties in determining whether a ML really develops in the spleen or whether this organ merely provides a suitable microenvironment for the proliferation of neoplastic lymphoid cells[19] have given rise to many different diagnostic criteria for these lesions. Some investigators include all ML with splenomegaly and cytopenia but without lymphadenopathy,[20] whereas others designate all ML with prominent splenomegaly as PMLS.[21] Still others abstain from the term PMLS and instead introduce "malignant lymphoma with prominent splenomegaly."[22]

To identify true PMLS among the cases of ML with prominent splenomegaly, Das Gupta and co-workers[23] have defined strict criteria which specify that a PMLS may only be diagnosed if spleen and splenic hilar lymph nodes but no other organs show neoplastic infiltrates. In the current study these criteria have been slightly modified and include cases with minimal liver and/or bone marrow involvement because ML initially developing in the spleen may easily spread to these organs.[24] This point is most convincingly illustrated by a variant of lymphoplasmacytoid lymphoma, the so-called "immunocytoma of the splenomegalic type."[18,20]

Using these diagnostic criteria and the updated Kiel classification of ML supplemented by immunophenotyping we identified 17 (3.4%) PMLS among 500 ML with splenic involvement. All of these were NHL, and, like in nodal ML, B-cell NHL outnumbered T-cell lymphomas.[25,26] Primary HD of the spleen was conspicuously absent; in fact, only very few cases of splenic HD have been reported so far and some of them are not adequately documented.[20,27-29]

The reasons for the infrequent occurrence of PMLS and the virtual absence of primary splenic HD are unknown. It may be argued that PMLS are underdiagnosed since due to their asymptomatic development and the relative inaccessibility of the spleen they escape detection long enough to disseminate. Thus, at the time of diagnosis they are no longer recognizable as PMLS. This assumption may hold true for some cases. However, the majority of splenic ML will eventually cause either splenomegaly with or without associated hypersplenism[29,30] and/or B symptoms which, as illustrated by our cases, will lead to their detection by modern imaging techniques.[31,32]

In fact, even smaller nodular splenic lesions such as hamartomas of the spleen give rise to early symptoms and are readily diagnosed.[33] Three of the cases in the current series apparently have been diagnosed even before dissemination from the spleen has occurred, since these patients exhibit a prolonged disease-free survival and may even be believed to have been cured by splenectomy.

In the current study several hypotheses concerning the reason for the infrequent occurrence of PMLS were tested. First of all, it could be postulated that PMLS are rare since the particular types of cells giving rise to the ML through neoplastic transformation are rare or absent in the spleen. This assumption is readily falsified, as the histologic and the immunophenotype indicate that PMLS represent "ordinary" ML which do not vary from their disseminated counterparts even with regard to their associated accessory cells, *e.g.*, interdigitating and follicular dendritic cells. At the same time, a ML derived from marginal zone cells, a cell type which occurs predominantly and in large numbers in the spleen has only rarely been positively identified.[34-36] Thus, it seems unlikely that the absence of a particular cellular component of lymphatic tissue prevents the development of PMLS. In addition the histologic features of PMLS do not differ from those observed in spleens involved by disseminated ML.[37]

Secondly, the scarcity of PMLS could be due to a lower proliferation activity of lymphatic cells in the spleen when compared with lymph nodes. This assumption has to be ruled out, since splenic lymphopoiesis[38] and proliferation activity[39] which in fact reflects the immunologic activity of the spleen's lymphatic tissue do not appreciably differ from lymph nodes and are unrelated to age or sex of the patients. In addition, proliferation activity of the ML as measured by Ki-67 staining[40] in several PMLS did not differ from the proliferation activity observed in splenic foci of disseminated ML of the same type. Another argument against this hypothesis may be raised by the existence of localized lymphoid hyperplasia in the spleen which may mimic ML[41] and of inflammatory pseudotumors which are associated with a high degree of proliferation and differentiation activity by splenic lymphatic cells.[42]

The last hypothesis tested in the current study states that the large numbers of potentially tumoricidal immunocompetent T-lymphocytes and macrophages in the spleen prevent the proliferation of neoplastic cells. If the degree of T-cell and macrophage infiltration is taken to represent a host cell response against the tumor[7,8] we could not demonstrate a statistically significant difference be-

tween PMLS and splenic foci of disseminated ML of the same type. However, our findings confirm previous reports that the number of reactive macrophages is higher in high-grade ML.[8]

In summary, the results of the current study indicate that (1) PMLS do indeed exist, albeit infrequently; and (2) the reasons for their rare occurrence are neither related to a low proliferation activity of lymphatic cells in the spleen nor to an overwhelming host response against the neoplastic cells. In addition, PMLS are not characterized by a distinct immunophenotype which might point to special histogenetic features. Further studies are needed to determine whether other properties of the neoplastic cells, *e.g.*, the presence of certain homing receptors[43] are associated with a primary presentation of ML in the spleen. Finally, the concept of PMLS despite the rarity of this condition is important clinically, since in PMLS splenectomy with or without adjuvant chemotherapy may achieve long-term remissions[44–46] and even definite cure.[3,47–49]

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