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PRIMARY SPLENIC LYMPHOMA: DOES IT EXIST ?

Paolo G. Gobbi, Giovanni E. Grignani, Ugo Pozzetti, Daniele Bertoloni, Carla Pieresca, Giovanni Montagna, Edoardo Ascari

Clinica Medica II, Dipartimento di Medicina Interna, Università degli Studi di Pavia, IRCCS Policlinico S. Matteo, Pavia, Italy

ABSTRACT

The number of primary splenic lymphomas being reported is increasing despite the rarity of this malignancy, but what really constitutes a lymphoma arising primarily in the spleen is still a matter of discussion. The authors choose the "restrictive" definition of a lymphoma involving the spleen and the splenic hilar lymph nodes only. In this way, the risk of epidemiologic or clinical overestimation is avoided.

The clinical features of this condition are characterized by non specific symptoms and signs, while the prevailing histology is that of a low-grade or intermediate-type lymphoma. Disease spreading outside of the spleen and its hilar lymph nodes is the single most important factor associated with an unfavorable prognosis.

From this usual clinical picture, two distinct nosologic entities can be outlined on the basis of histologic and immunologic peculiarities: splenic lymphoma with circulating villous lymphocytes and marginal-zone splenic lymphoma. The former arises from follicular center cells and is characterized by hypersplenism, variable percentages of circulating villous lymphocytes and, frequently, a monoclonal gammopathy. The latter originates from a peculiar splenic B-cell structure separated by the mantle zone. The proliferating cells are medium-sized KiB3-positive lymphocytes with round or cleaved nuclei and pale cytoplasm, which surround follicular centers and infiltrate the mantle zone. It is interesting that marginal-zone lymphoma cells share some of the characteristics of the lymphocytes involved in both lymphomas of mucosa-associated lymphoid tissue and the B-monocytoid lymphomas. Splenectomy is still the most effective therapy for all primary splenic lymphomas.

Key words: primary splenic lymphoma, circulating villous lymphocytes, marginal-zone lymphoma, splenectomy

How primary splenic lymphoma is currently defined

It is well known that diagnosing as *primary* in unusual sites neoplasias that commonly arise elsewhere or are already diffuse when discovered is strictly related to the accuracy of available diagnostic means.

At present, the definition of primary splenic lymphoma (PSL) is still used ambiguously in the literature, so that inaccurate observations and series reviews adopting loose selection criteria are found. This is undoubtedly due to the absolute rarity of this presentation, as occurs for many other organs of uncommon primary involvement such as the liver, bone, stomach and central nervous system.

For this reason we fully agree with Das Gupta et al.,[1] who adopted a restrictive definition of PSL as a lymphoma involving only the spleen and the splenic hilar lymph nodes.

Although the spleen is involved in more than half the patients affected by Hodgkin's disease (HD), in about a third of those with non-Hodgkin lymphomas (NHL), and although very many cases of primary splenic involvement have been reported, quite often the disease is at

Correspondence: Paolo G. Gobbi M.D., Clinica Medica II, Dipartimento di Medicina Interna, Università di Pavia, IRCCS S. Matteo, 27100 Pavia, Italy.
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most prevalently, but not exclusively, localized in the spleen and its hilar lymph nodes. On the other hand, many authors have observed that PSL tends to be asymptomatic until the disease spreads. So, in their opinion, too restrictive a definition can lead to a certain degree of casuality in its diagnosis and a substantial underestimation of its true incidence.

Thus, some authors accept as sufficient for defining a lymphoma as primary splenic that the bulk of the neoplasm be localized in the spleen, although other organs (i.e. lymph nodes, liver and bone marrow) may also be infiltrated. According to this interpretation, Kraemer, Osborne and Butler,[2] on the one hand, excluded bone marrow involvement in their 49 patients, while, on the other hand, they accepted liver and lymph node involvement. Similarly, Kehoe and Straus[3] in their series of 21 patients included 14 with liver, bone marrow or abdominal lymph node involvement, although they did correctly distinguish this patient group in their analysis of clinical features. Falk and Stutte[4] in their retrospective series of 17 also included patients with minimum liver and bone marrow involvement, which, according to them, did not alter the *primariness* of the disease. They support this interpretation because of the ease with which lymphoma spreads to both these sites; however, they do not specify what they consider minimum infiltration.

On the contrary, in our opinion, concern about making the criteria for defining PSL less restrictive, so as to accept cases that may be widely diffuse but of likely splenic origin, does not respond to the need for a more correct epidemiologic and nosologic evaluation. Indeed the current practice of examining the entire organ after splenectomy to diagnose PSL represents a limitation on correct epidemiologic quantification, because resection of this organ is not necessarily required unless particular problems are encountered. Therefore it is obvious that PSL is often recognized after it has spread to other sites and not because splenectomy was performed, so by definition this cannot be considered primary splenic lymphoma. There are several reasons for this: a) biopsy of other organs involved secondarily allows a diagnosis to be made; b) splenomegaly often does not become a clinical problem or cause complications; c) splenomegaly is minimum or absent, even though the spleen is affected by the lymphoma.

It is evident that as long as splenectomy is necessary to diagnose PSL and as long as surgical exploration of the entire abdomen is the only instrument available for excluding involvement of other organs, the true incidence of PSL – if this entity exists – will continue to be underestimated. Moreover, we will only be able to have certain knowledge about the very initial stage of the disease course when just the spleen is involved (the current prerequisite for talking about PSL). In the future we will have greater possibilities for early diagnosis when new imaging techniques capable of resolution limits of a few millimeters (for both lymph nodes and viscera) become available. At present, we should also re-evaluate the use of percutaneous splenic biopsy guided by ultrasonography or computerized tomography to increase diagnostic accuracy. This procedure has became increasingly less popular in the last 15 years – probably due to Anglo-Saxon scientific literature – while it was considered relatively sure and was extensively utilized throughout Europe until the '70s.[5,6]

At present the wisest decision for all researchers would be to resist the temptation to affirm the primariness of splenic involvement, because up to now such a definition has not either extended our knowledge of the disease or improved therapeutical criteria and results. It would be very useful to adopt Ahmann's criteria[7] (see Table 1). This researcher approached the problem from a clinical point of view and distinguished 3 different types of involvement among splenic lymphomas: I) spleen alone; II) spleen and splenic lymph nodes; III) extension to liver and to lymph nodes other than splenic hilar (and, as wisely suggested by Kehoe and Straus, bone marrow involvement should also be added). The advantage to these criteria is the possibility of keeping clearly primitive cases (groups I and II) separated from those which would become merely presumed splenic lymphomas (group III).

Table 1. Primary splenic lymphoma staging.

Stage I:	spleen involvement only	corresponding to the restrictive definition of PSL
Stage II:	spleen and hilar lymph node involvement	
Stage III:	extension to other abdominal lymph nodes and/or viscera	only presumed to be PSL

Pathological and clinical study could be usefully extended to all *malignant lymphomas presenting with prominent splenomegaly*, a term which seems more correct than PSL for group III lymphomas. In the meantime we should continue to watch for possible special nosological entities in those situations where splenic origin of the lymphoma seems at least plausible since some new forms have recently been singled out, as will be discussed below.

General characteristics of primary splenic lymphomas

After these general considerations, which were necessary from the point of view of both terminology and methodology in order to point out the biases and ambiguities in the scientific literature, it must be stressed that PSL is rare but relatively more common in NHL than in HD.

Although HD has been found to involve the spleen from the onset in up to a third of patients undergoing explorative laparotomy,[8] primary splenic localization has been observed in very few cases. Nevertheless, these cases were unquestionably primarily splenic,[3, 9-11] and are particularly interesting because they demonstrate that HD may truly originate in the spleen. In the past this possibility was not given enough consideration when one of the principal aims was to understand the diffusion routes of the disease, and one of the still unexplained questions was how the disease could reach the spleen since this organ has no afferent lymphatic vessels. Indeed, given the fact that disease spread should have been hematogenous, it was difficult to explain the low rate of relapse in liver, bone marrow and lungs – targets no less subject to hematogenous micrometastasis – in stage IIISA patients treated only with radiotherapy. For the same reasons mentioned above, it is likely that primitive development of HD in the spleen is underestimated by present staging techniques, explorative laparotomy included. Moreover, this peculiar primary localization could explain some of the anatomical routes of disease spread otherwise difficult to understand.

Cases of PSL are more numerous in NHL, although they are often very heterogeneous with regard to clinical and histological evaluation. These cases are the result of two different research aims: the first is directed toward ascertaining possible differences in clinical and histological presentation, as well as in prognostic characteristics of PSL with respect to lymphomas arising in other sites; the second is directed at identifying and outlining possible forms of PSL whose characteristics are completely different from the majority of other PSL and/or from those of lymphomas arising in other sites.

In most series reported in the literature the prevailing histology (more than 50% of cases) is that of a low-grade lymphocytic lymphoma (well differentiated small cell variant or with lymphoplasmocytic/lymphoplasmocytoid differentiation[2,12]), or intermediate-grade lymphoma (diffuse or nodular mantle-zone lymphoma[13]). It has been stressed this is probably not the true incidence or distribution of PSL, because even well-trained pathologists have trouble distinguishing small-cell lymphoma from reactive lymphocyte proliferation. The miliary appearance of small-cell lymphoma in

which the white pulp is uniformly involved is extremely similar both macro- and microscopically to benign immune reactions.

Predominantly small cleaved cell follicular lymphoma is recognizable by the presence of nodular growths in white pulp composed of a relatively pure population of cleaved small lymphocytes; these cells quite often also infiltrate the red pulp (which generally has few small lymphocytes around the arterial capillaries), and this can be a useful sign for distinguishing lymphoma from a benign reactive form, although it is not an absolute criterion.

Paradoxically it has been pointed out[12] that even a scanty infiltration of small lymphocytes in the portal spaces or in the bone marrow is helpful in diagnosing a splenic lymphoma. It is quite obvious that such a criterion represents another limit to recognizing the primariness of splenic involvement.

PSL, in the two histotypes already described, presents a clinical picture characterized by non specific symptoms and signs, and in most cases the lymphoma has already spread beyond the spleen. Abdominal pain in the upper left quadrant, weight loss, fatigue, anorexia, fever and night sweats are the most common disturbances. Rarely, it may also be asymptomatic. Intermediate-grade lymphoma shows a greater incidence in females and prognosis, after splenectomy and chemotherapy, is slightly worse than that of well-differentiated small-cell lymphoma.

In recent series and in single-case reports whose authors adopted restrictive diagnostic criteria,[4,14-17] the prevalence of small-cell lymphoma histotypes is clear. The 27 patients involved in these studies were categorized as follows: 9 well-differentiated small-cell lymphomas, 4 predominantly small cleaved cell follicular, 3 predominantly large cell follicular, 2 large cell lymphomas, 3 immunoblastic large cell, 1 peripheral T cell lymphoma, 4 pleomorphic lymphomas (1 small cell, 1 intermediate cell, 1 large cell and 1 T-cell lymphoma), and 1 plasmocytoma.

If a patient belongs to one of the first two Ahmann groups (lymphoma limited to the spleen or extending only to the hilar splenic lymph nodes), the disease generally has a rather good prognosis regardless of the tumor's histology. In the Kehoe and Straus' series,[3] group I and II patients enjoyed a median survival of 82 months, while group III members survived for a median of 24 months. Current therapy varies widely among the cases reported and the literature provides no indications nor even any suggestions as to what might be the best approach following splenectomy in a primary splenic presentation.

Possibly true primary splenic lymphomas

While the above-mentioned are the general characteristics of PSL, there are nevertheless two distinct nosologic entities that, although uncommon, have been distinguished from the usual picture in the last few years. *Splenic lymphoma with circulating villous lymphocytes*, which originates from follicular center cells, has been reported sporadically by different authors[18-21] and was thoroughly characterized by clinicians and pathologists from our institution.[22] The second type is *splenic lymphoma of the marginal zone*, a structure found in the mammalian spleen only when an important B cell area is separated by the mantle zone.[23]

The principal features of splenic lymphoma with circulating villous lymphocytes are the following: outstanding splenomegaly, which dominates the overall clinical picture, a certain number of lymphocytes that stain positively for tartrate-resistant acid phosphatase and present cytoplasmic projections that can appear like tufts of hair under ideal conditions of observation. This lymphoma usually affects people in advanced age, and the clinical picture is characterized by hypersplenism with anemia and thrombocytopenia, but without either changes in the white cell count or an increase in the frequency of infections. A monoclonal gammopathy whose plasma concentration usually remains below 20 g/L is present in about 2/3 of such patients, and only rarely are light chains detected in the urine.

Morphologically,[24] villous lymphocytes are slightly larger than the typical standard lym-

phocytes of cronic lymphocytic leukemia (CLL). They are comparable in size to cells of prolymphocytic leukemia (PLL) and have a round nucleus with a single evident nucleolus in 40-90% of cases. The cytoplasm is variable but is generally clear and abundant, sometimes distinctly basophilic, with irregularities in the cytoplasmic border due to short thin villi distributed around the whole cell or concentrated at one of its poles. Phase contrast microscopy examination makes this latter aspect much more evident. About 3 to 23% of these cells stain positively for alkaline phosphatase. This reaction is of medium intensity and the resulting pattern shows granules that can be indifferently small, large or scattered. This alkaline phosphatase positivity is resistant to L-tartrate. Villous lymphocytes show a B-phenotype that is strongly positive for surface immunoglobulins. They also express the antigens CD19, CD20, CD22, and CD24. On the contrary, they are negative for the CD5 and CD23, which are commonly positive in CLL. They usually do not express the antigens CD11c, CD25, HC-2 and B-ly-7, which characterize hairy cell leukemia (HCL).

The spleen is usually greatly enlarged and has a smooth capsule. Sectioning reveals numerous nodules with diameters ranging from 1 to 10 mm. These nodules present a mixed population of small, medium and large-sized cells. The large ones are immunoblasts with occasional Reed-Sternberg cells. The small and medium-sized ones are cleaved lymphocytes, small lymphocytes and rare lymphoplasmocytoid elements. Small lymphocytes infiltrate red, cord and sinus pulp.

Lymph nodes are usually infiltrated by small and medium-sized lymphocytes. Sometimes scanty lymphoplasmocytoid cells are present. The great majority of these patients show a nodular infiltration of lymphocytes in the bone marrow. In such cases bone marrow aspiration readily yields material, contrary to what happens in HCL.

Three diseases characterized by splenomegaly must be considered in the differential diagnosis: HCL, PLL and CLL (see also Table 2).

Hairy cell leukemia. It is most uncommon for this disease to be accompanied by a monoclonal gammopathy. Moreover, villi are more randomly distributed around the whole cell rather than being concentrated at one pole as in PSL. There is generally leukocytosis with circulating lymphoplasmocytoid cells.

Table 2. Diagnostic criteria for PSL with circulating villous lymphocytes.

Immuno-phenotype		*Clinical and morphological features*	*Histochemical features*
sIg	+	Cells larger than usual CLL lymphocytes	Alkaline-phosphatase L-tartrate resistance
CD19	+		
CD20	+		
CD22	+	Round nucleus with a single nucleolus	
CD24	+		
CD5*	–		
CD23*	–	Cytoplasmic projections mostly but not exclusively at one pole of the cell	
CD11c°	–		
CD25°	–		
HC-2°	–		
B-ly-7°	–	Monoclonal gammopathy in about 70% of cases	

*Differential criterion between CLL and PSL.
°Differential criterion between HCL and PSL.

Prolymphocytic leukemia. This form of leukemia presents a striking leukocytosis that generally exceeds 100×10^9 cells/L. Circulating cells can resemble villous lymphocytes for the dimensions of the nucleus and cytoplasm. There is also a nucleolus sometimes, but the cells do not show villous projections. Moreover, the clinical course is rapidly progressive, while PSL is a rather indolent disease.

Chronic lymphocytic leukemia. The purely splenomegalic form must be differentiated from PSL with villous lymphocytes when the latter shows small cells with scanty cytoplasm, small nucleous and one, two or no nucleoli. In this case demonstration of the villous projections with either a phase contrast or electron microscope is essential. Lastly, CLL cells are intensily positive for CD5, while villous lymphocytes are negative for this antigen.

PSL with villous lymphocytes responds well to therapy;[25] 28% of patients do not require any treatment and follow an indolent (often entirely asymptomatic) clinical course for years.

About 40-50% of patients undergo splenectomy eventually, and this produces a complete remission that lasts from 6 months to 7 years. This outcome is independent of the stage of the disease at which it is undertaken. In other words, splenectomy gives excellent results both as first-line therapy and as a second or even third-line measure. Good results are also obtained with radiotherapy. A dose of 1000 cGy in 2 weeks gives a fair outcome, especially if one considers that such treatment is usually reserved for patients who have a high surgical risk or who have become resistant to chemotherapy.

Chemotherapy usually concists of chlorambucil plus glucocorticosteroids and is often given in pulses. This association produces a complete and durable response in up to 45% of patients, even when given as first-line therapy without splenectomy. Chemotherapy with 3 or 4 drugs: COP (cyclophosphamide, oncovin, prednisone) and CHOP (COP+adriamycin) has yielded more equivocal results.

Overall survival in one of the best case studies[25] of PSL with villous lymphocytes showed 82% and 78% of patients alive at 3 and 5 years, respectively.

The principal distinctive characteristics of the rarer *splenic lymphoma of the marginal zone* are essentially cytologic and histologic. Since the marginal zone external to the follicle is particularly well defined in the spleen, it is not strange that the first reported cases of marginal-zone lymphoma likely originated from the spleen. Analogous structures are also seen in Peyer's patches and in secondary lymph node follicles.

So far 4 cases have been described:[23] 4 women whose ages ranged from 43 to 72 years. Initial symptoms were caused by splenomegaly and anemia. The lymphoma had already spread to the bone marrow at diagnosis in all 4 patients. Only one woman presented generalized lymph node involvement. The follow-up for these patients is very short, from 4 to 12 months. Three are in complete remission following only splenectomy. The fourth, with generalized lymphadenopathy, died in disease progression 1 year after splenectomy, even though she was treated with adjuvant chemotherapy.

The surgically removed spleens weighed from 1,160 to 1,840 g and showed multiple greyish nodules with diameters of from 2 to 9 mm. The hilar lymph nodes were always involved.

Splenic histology is characterized by wide concentric cords of medium-sized lymphocytes with a round or cleaved nucleus and a fair amount of pale cytoplasm. These cells surround the follicular center and sometimes infiltrate the mantle zone or the follicles themselves. Normal histologic architecture is absent both in the nodules and throughout the organ. Bone marrow infiltration is paratrabecular and cells lack the following antigens: CD5, CD10 and CD23. They are positive for antibody KiB3, which identifies an isotype of the common leukocyte antigen (B lineage marker). This antigen is not usually expressed by mantle-zone cells. There is a rearrangement of the immunoglobulin heavy chain genes but not of bcl-1 and bcl-2. This is in contrast to what happens in follicular, intermediate and mantle-zone lymphomas.

These morphologic and immunophenotypic characteristics induced some authors[27] to associate the origin of these neoplasms with MALT (*mucosa-associated lymphoid tissue*) lymphomas and with B-monocytoid cell lymph node lymphomas, also because of the partial and selective substitution of the germinal center, called *follicular colonization*. MALT lymphomas have a completely different clinical history with respect to marginal-zone lymphomas, since the former tend to remain confined to digestive structures. The differences between marginal-zone and B-monocytoid lymphomas are subtle and shaded. They share a marginal localization, a relatively indolent clinical course (but with a sure tendency to spread in different organs) and the principal immunophenotypic characteristics. The antigenic pattern is distinguishable by the latter's positivity for CD25 and negativity for CD35 in B-monocytoid lymphoma, while the contrary is true for marginal-zone lymphomas. This discrepancy probably results from different activation conditions for the same cell lineage. It seems reasonable that the two represent the same nosologic entity with minimal functional differences according to the

splenic or lymph node origin of the cell. As with other splenic lymphomas, when marginal-zone lymphomas originate in the spleen the earlier splenectomy is performed the more effective this treatment is, and the less effective it becomes if the disease is widespread.

The so-called *primary splenic lymphoplasmocytic lymphoma lupus anticoagulant-associated*, of which there are very few reports[28] does not seem to be a separate nosologic entity. This lymphoma is thought to be characterized by splenomegaly as the predominant or only sign, and to be the results of a lymphoplasmocytic infiltration that generally involves the bone marrow and liver as well. An IgM monoclonal gammopathy is reported to occur relatively frequently. Its high concentration (≥ 4 g/dL) gives rise to a characteristic thrombotic diathesis in both the venous and arterial systems. As a matter of fact, if we do not consider the problem of splenic primariness, the characteristics listed in the case reports are perfectly consistent with a diagnosis of Waldenström's macroglobulinemia (WM). Indeed splenomegaly is not an unusual sign in WM; lymphoplasmocytoid infiltration, monoclonal component in high concentration, and its potential pleomorphic antibody activity – sometimes directed against coagulation factors or electronegative phospholipids or other targets – are all well-known disturbances typical of WM.[29] The only peculiarity, and even this is not so exceptional, would be the remarkable splenomegaly. So, we suggest talking simply of a *hypersplenomegalic WM*, and not of a new *PSL with lymphoplasmocytoid histotype and monoclonal IgM gammopathy with lupus-like anticoagulant activity*.

Furthermore, interference with coagulation is intrinsically possible for almost all monoclonal gammopathies (even those other than IgM) that may be found in various kinds of lymphomas.[30]

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