Treatment of splenic lymphomas

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A B S T R A C T

Virtually all node-based non-Hodgkin lymphomas can disseminate to the spleen; however, in some particular lymphoma types the spleen is the predominant site of involvement at diagnosis, which gives rise to clinical pictures characterized by splenomegaly and absent or unnoticeably lymphadenopathy. Such a peculiar clinical presentation in the past fostered an unproductive debate focused on defining the amount and anatomical distribution of the extra-splenic disease that allowed qualifying a lymphoma as a primitive splenic lymphoma (SL). Actually, most cases of "primitive" SLs show some degree of bone marrow infiltration and even variable spillover of neoplastic cells into the peripheral blood. Therefore, any operative definition of SLs should encompass cases presenting as confined within the spleen, and cases in which the disease extends also to the bone marrow, the peripheral blood, and/or the liver, in the absence of conspicuous lymph node involvement. Undeniably, such a categorization of SLs would comprise a wide and heterogeneous array of diseases, whose clinical behavior spans from indolent to highly aggressive. Nevertheless, the presenting clinical, laboratory, and pathological features, and the therapeutic strategies that often comprise splenectomy, display significant overlaps, which justify grouping diverse entities under the same "operative heading" of SLs.

The Ill-Defined and disputable boundaries between "Spleen involvement" and "Splenic lymphomas"

Spleen involvement in non-Hodgkin's lymphomas (NHL) is a rather common event as part of the disease's natural course and dissemination.[1] Conversely, the spleen only rarely represents the main site of the lymphomatous burden at disease onset, which would suggest a potential splenic origin of the neoplasm.[2-5]

The heterogeneous group of NHL which, upon presentation, appear confined to the spleen or display a predominant splenic involvement in the absence of significant nodal disease, falls within the fringes of splenic lymphomas (SLs). Actually, the definition of SLs does not imply an histogenetic origin of the lymphoid clone from the spleen,[6] which is indeed questionable in most cases, rather it reflects the requirement for a common diagnostic workup dictated by shared clinical presentations in which peripheral cytopenia(s) and/or splenomegaly may be the only signs.[7]

Within the above discussed definition of SLs, two subgroups of lymphoid neoplasms can be identified according to the attitude of the neoplastic clones to home the bone marrow (BM) parenchyma.

The first of the two subgroups includes cases that can be properly defined are as primary splenic lymphomas (PSLs), in which the neoplastic clone is confined to the splenic parenchyma with the sole exception of hilar lymph nodes.

The second group of cases, which we refer to as "spleno-medullary" lymphomas (SMLs), comprises lymphomas in which splenic involvement is paralleled by BM infiltration, with or without involvement of other vascular niches, such as the hepatic one. In this latter group of cases, the peripheral blood involvement ranges from an inconsistent spillover to a frank leukemic picture.[4-6,7]

SLs represent nearly 6% of all NHL and encompass a wide array of diseases with diverse clinical behavior spanning from indolent to highly aggressive.[7] The splenic presentation is the rule for some pathological entities, such as Splenic Marginal Zone Lymphoma (SMZL),[8] or rather it represents a rare clinical variant for other lymphomas that usually arise in the lymph nodes, such as follicular lymphoma (FL). A list of NHL that may present as SLs is reported in Table 1.

The rarity of SLs has deeply influenced the availability of biological data, even contributing to blurring the borders between specific nosographic entities (*e.g.*, SLs/leukemias unclassifiable),[9-10] and impairing the standardization of therapeutic approaches, which so far remain mostly based on anecdotic reports, retrospective analyses, or small phase II studies.

Moreover, in spite of the shared presentations and clinical findings showing considerable overlap, SLs have little in common as far as their therapeutic strategies are concerned.

In this paper, the diagnostic and therapeutic challenges of prototypical entities included under the definition of SLs will be discussed.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is an aggressive B-cell neoplasm commonly displaying a

mixed nodal and extranodal presentation.[11] It has been recognized that some cases of MCL show the clinical picture of SMLs characterized by splenomegaly, bone marrow involvement, variable degree of lymphocytosis, and inconspicuous lymphadenopathy.[12,13] Such an unusual splenic MCL presentation accounts for about 20-40% of the extranodal MCL cases[14] with patients experiencing a less aggressive disease course allowing prolonged survival, often exceeding 7-10 years.[11]

Whether these splenic MCL cases represent the expression of the most favorable end of MCL clinical spectrum or a distinct biological variety remains unclear, even if distinct bio-molecular features (*i.e.*, hypermutated IGVH genes, non-complex caryotypes, distinct GEP signature, lack of SOX11 expression) are in favor of the latter hypothesis.[11,15]

However, not all the splenic MCL actually pursue an indolent course, therefore, the upfront identification of patients who will experience a rapidly progressive disease is of utmost importance and still represents a challenge. Data on the therapeutic approach of these splenic forms of MCL are scarce but some evidence suggests that asymptomatic patients with low MIPI score can be considered for a watchful-waiting approach that allows deferring treatment until symptomatic disease development, for a median time of about 12 months (range 4 to 128).[16,17] Notably, Martin *et al.* showed that while time to treatment was not predictive of patients' overall survival in multivariate analysis, patients within the observation group fared better than those included in the early treatment group in terms of overall survival (not reached *vs.* 64 months, P=00.4). Based on this picture, it might possibly be envisaged that patients included in the observation group have a less aggressive disease.[11,16-18]

In the setting of splenic MCL patients, the axiom that symptoms related predominantly to splenomegaly and/or cytopenia(s) may be managed efficiently through splenectomy, likely holds true.[19,20,21] Indeed, splenectomy has been reported as an effective palliative treatment in both naïve or relapsed/refractory MCL patients, producing complete resolution of splenomegaly-related symptoms, amelioration of peripheral cytopenias, and prolonged treatment-free interval (12-94 months) in most patients.[14,19-21]

Following splenectomy, complete resolution of thrombocytopenia and anemia has been reported in 69 and 90% of patients, respectively. Interestingly, in most patients, a downward trend in neoplastic lymphocyte count can be scored after splenectomy, suggesting a central biological role for the splenic environment in the growth and progression of this lymphoma.[19,20]

Other open questions are whether splenic MCL patients would benefit from being treated upfront despite being asymptomatic, and if high-dose Ara-C containing chemotherapy followed by autologous transplantation, as indicated for "standard" MCL patients[11] or a gentler therapeutic approach[22,23] should be considered as the reference treatment in this setting.

Diffuse large B-cell lymphomas

Diffuse Large B-cell lymphomas (DLBCLs) of the spleen are rare lymphomas accounting for 11% of all

Table 1. Lymphoid malignancies that may present as SLs.

*Lymphomas commonly/typically presenting as SLs**
SMZL
SL-u
Splenic Diffuse red pulp-B cell lymphoma
HCL variant
HCL
B-PLL
T-LGL
Hepatosplenic T-cell lymphoma
Primary splenic presentation of nodal lymphomas
MCL
FL
DLBCL not otherwise specified
Micronodular T-cell/ histiocyte rich large B-cell lymphoma

*Splenic presentation encompasses cases with splenic involvement and in which the disease may extend also to the bone marrow, peripheral blood and liver in absence of prominent lymph nodes involvement.

SLs.[24,26] They may present either as PSLs or SMLs and can be divided into three main types according to the pattern of splenic involvement: macronodular, micronodular, and diffuse (of the red pulp).[27]

Splenic lymphomas with a macronodular pattern mostly presents as PSLs; macroscopically, the neoplastic lesions appear as solitary or multiple partially coalescent large nodules occupying most or the whole splenic parenchyma and display histological, immunophenotypic, and biomolecular features overlapping those of their nodal counterpart. The splenic parenchima free from lymphomatous infiltration appears normal, although in a subset of cases, infiltration of the splenic capsule, hilar lymph nodes, and adjacent structures can be observed. Accordingly, the majority of patients are diagnosed in stage I-II.[28,29] Splenomegaly is the predominant clinical finding, though nearly one-third of patients also complain of constitutional symptoms and/or left flank discomfort or pain.[27] PSLs with macronodular pattern show a relatively favorable outcome in line with that of other forms of DLBCL diagnosed in limited stage. In the largest study reported so far, splenectomy and systemic therapy achieved that 15 out 20 patients were alive and 13 of them in complete remission after 7-120 months of follow-up.[27]

Micronodular infiltration is the second most common pattern of splenic DLBCLs.[27,30] A huge splenomegaly is a constant finding, and most patients are symptomatic and show a variable degree of anemia. The spleen shows a relatively uniform miliary pattern engendered by white pulp centered tumor nodules ranging from 0.5-4 cm in diameter, with variable infiltration of the red pulp. Commonly, the histological features are those of DLBCL and in most cases, the lymphoma is confined to the spleen. The reported outcome is less favorable compared with that of cases presenting with a macronodular infiltration pattern.[27] In a minority of cases, the infiltrating nodules can be barely or not visible on gross examination of spleen cut surface and histologically contain a variable number of neoplastic B-cells scattered in a background of T-lymphocytes and histiocytes resembling the T-cell/histiocyte rich variant of DLBCL.[30-33] Whereas the tumor bulk is in the spleen, neo-

plastic cells infiltrate the bone marrow constantly and frequently the liver sinusoids and the pulmonary interstitium while usually sparing the lymph nodes. These splenic DLBCL cases affect predominantly middle-aged men who experience an aggressive disease course marked by B symptoms, variable degree of peripheral cytopenia, and huge splenomegaly, with most patients dying of the disease within 2 years from diagnosis.[31] The majority of cases so far described received standard anthracycline-based chemotherapy and were splenectomized for diagnostic purposes. For this reason, the therapeutic role of splenectomy in these patients still remains unchallenged, as it is the potential role of rituximab addition to chemotherapy.

Cases of DLBCL marked by a diffuse splenic red pulp infiltration are extremely rare and most reports are relative to Asian patients.[27,34-37] The neoplastic cells diffusely and loosely infiltrate splenic red pulp cords and sinuses, moreover, liver and bone marrow are frequently infitrated on presentation, and the neoplastic cells can be detected in the peripheral blood in about 50% of cases. Tumor cells with a centroblast, polylobated centroblast, or pleomorphic appearance show in more than 80% percent of cases' immunophenotypic features of "activated B-cell type" DLBCLs, and may dimly express CD5. Signs of hemophagocytic histiocytosis in the bone marrow are frequently detected, even if the development of an overt hemophagocytic syndrome is infrequent.[37] Importantly, the clinical presentation of patients with splenic DLBCL with diffuse red pulp involvement can mimic that of infective diseases owing to the almost constant occurrence of hepato-splenomegaly, fever, and cytopenia.

Follicular lymphoma

Follicular lymphoma (FL) is the most frequent nodal lymphoprolypherative disorder. In less than 10% of cases, FL arises in extranodal sites and among these sites, the spleen is by far the less frequent.[38] However, in two large tertiary centre series, FL accounted for 12% of all the lymphoid neoplasms diagnosed in the spleen.[39] Only few reports have so far focused on follicular SLs, and a rather heterogeneous picture has emerged as far as the biology of this peculiar FL presentation is concerned. Actually, most of the cases of primary splenic FL reported by Mollejo *et al.*[40] were characterized by BCL2 and/or CD10 negativity (8 of 9 cases and 4 of 9 cases, respectively) and by the absence of BCL2 translocation (8 of 8 cases), as well as by a high proliferation index (7 of 9 cases) and rate of transformation toward DLBCL (3 of 8 cases). Conversely, all the cases of splenic FL reported by Howard *et al.*[41] displayed biologic features paralleling those of nodal FL cases.

All the cases of primary splenic FL included in these two series underwent diagnostic splenectomy, which was followed by either watchful waiting or systemic therapy ranging from anthracycline-based therapy to stem cell transplantation, with rituximab being administered in only three patients as monotherapy.[40] At present, there is not sufficient evidence of a diverse biologic and clinical behavior of primary splenic FLs to support the adoption of treatment strategies diverging from those of nodal FLs.[42] Hence, the association of rituximab and polychemotherapy, whether or not preceded by splenectomy, can be considered as a reasonable treatment for this setting of patients.

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HCTCL) is a very rare and aggressive neoplasm whose supposed normal cell counterpart is a peripheral γδ1 (or less commonly αβ) T-cell of the innate branch of the immune system.[43,44]

HCTCL is extremely rare, accounting for less than 1% of all NHL, and its peak of incidence is in the second to third decade of life, with a striking prevalence in men (male:female ratio 9:1). Up to 20% of cases arise in patients with history of autoimmune diseases or in the setting of immune system impairment.[45-49] Indeed, patients undergoing solid organ transplantation and young patients with chronic inflammatory bowel diseases who receive long-term immunosuppressive treatments with the association of thiopurines and anti-TNF have been reported to show a significantly increased risk of developing such a neoplasm. Yet, the increased risk associated with these conditions only impacts HSTL barely, with a very low incidence.

HSTCL presents constantly as a SML with neoplastic cells showing predominantly an intrasinusoidal pattern of bone marrow infiltration, which is maintained even upon disease progression.[43,50]

On presentation splenomegaly is invariably observed and in the majority of cases, a certain degree of leukemic spread can be detected. Abdominal pain, constitutional symptoms, particularly fever, abnormalities in liver function tests, and cytopenia(s) are the most frequent presenting features delineating clinical pictures that can be hardly accountable to such a rare a lymphoma being reminiscent of infective or liver diseases.[50,52] Constitutive BM infiltration at presentation can support the early development of hemophagocytic histiocytosis with overt hemophagocytic syndrome complicating the clinical presentation and the disease course.[44-50-53]

Because HSTCL may actually mimic more frequent systemic diseases, and since the histopathological picture of the lymphomatous infiltrates outside the spleen may be elusive, it is crucial to plan promptly and interpret correctly the appropriate diagnostic tests to include this exceptionally rare lymphoma in the array of differential diagnoses of young patients presenting with constitutional symptoms and splenomegaly.

BM and liver histology complemented by immunophenotypic analysis coupled with cytological and immunophenotypical examinations of peripheral blood can be highly informative and even lead to the correct diagnosis, avoiding unnecessary and possibly harmful surgical procedures.[43,50] However, it should be underlined that the subtle intrasinusoidal infiltrate within the BM parenchyma can be overlooked in the absence of positive findings of T-cell-associated markers (*e.g.*, CD2, CD3) on immunohistochemistry, and hyperplasia of the myeloid marrow can be misleading, suggesting a diagnosis of reactive hyperplasia or myelodysplasia.[53,54]

The exiguous amount of literature about HSTL, which is mostly constituted by single case reports with a short observation time, is the main obstacle to the drawing of

therapeutic strategies for the clinical practice.

Although some patients have been reported to experience a relatively indolent course, the clinical behavior of this neoplasm is typically very aggressive, allowing median survival times shorter than 2 years.[50-52] Splenectomy has little, if any, role in the palliation of HSTL patients because its efficacy in ameliorating peripheral cytopenias may be flawed by the rather frequent occurrence of hemophagocytic histiocytosis in the bone marrow sustained by the conspicuous cytokine secretion of residual neoplastic cells and by the rapid progression of tumor infiltrates outside the spleen. Nevertheless, splenectomy might be considered in some selected cases as the first therapeutic step aimed at ameliorating severe cytopenias in view of intensive systemic treatment.[53,55]

Treatment with anthracycline containing chemotherapy produces short-lived clinical responses in about 60% of patients who eventually die of progressive disease within 2 years (median OS 8-16 months).[50-52]

Only a minority of the patients reported in the literature survived longer than 36 months of diagnosis, and most of them had received first-line therapy with platinum and/or high-dose cytarabine and autologus or allogeneic bone marrow transplantation as consolidative therapy while in CR.[50,51,56]

Moreover, patients enjoying relatively long survival times, which were attributed to the beneficial effects of transplant procedures, have been described in single case-reports.[57-59] Among the different first-line, non anthracycline-based, therapies described in anecdotic reports or small series, promising yet transient responses have been obtained with 2-deoxycoformycin alone or in association with alemtuzumab.[53,57,60-62]

The rapid progressive nature and therapy resistance of HSTL clones suggest that young and fit patients who attain a CR following induction chemotherapy should be consolidated with BEAM conditioning and ASCT and subjected to allogeneic transplant.

Splenic marginal zone lymphoma

Splenic marginal zone lymphoma (SMZL) is a relatively rare neoplasm accounting for 1-3% of all NHLs but it represents the most frequent lymphoma presenting in the spleen. SMZL was first described in 1992[63] and since then, its clinical, biological and histological features have been delineated in several large series[64-70] that provided the basis for its inclusion as a definite entity in the latest WHO classification.[71]

The peak of incidence of SMZL is in the seventh decade of life and, at variance with other mature B-cell lymphoprolipherative disorders, it is more frequent in female subjects. SMZL almost constantly presents as SML, showing bone marrow infiltration (83-100%) and the presence of an overt leukemic component (29-75%) already at diagnosis. In nearly 20% of cases, deep sited abdominal small lymphoadenomegaly can be detected. Up to 30% of patients are completely asymptomatic on presentation and often ask for medical assistance following the detection of an isolated splenomegaly.[8,72] When symptoms are present, they are usually related to the abdominal discomfort secondary to splenomegaly, to peripheral cytopenias, (anemia 48%, thrombocytopenia 24%), autoimmune manifestation (9%), or to a combination of the above signs.[73]

The diagnostic gold standard is the histological examination of the spleen.[71] However, the integration of data obtained from peripheral blood and BM investigations may lead to a definite diagnosis of SMZL in the absence of diagnostic splenectomy in a considerable percentage of patients.[72] Although a "splenectomy sparing" diagnostic approach has never been prospectively validated, it is widely believed to have a high diagnostic accuracy (>80% of cases). SMZL commonly pursues a true indolent course allowing a median survival time ranging from 9 to 13 years.[73] However, while most patients do not require any therapy for several years and eventually die of causes unrelated with the lymphoma, 20-30% of patients display a less favorable outcome[74] (56% of patients alive at 5 years) and in 13-19% of cases, the neoplastic clone undergoes histological progression towards a DLBCL in the bone marrow, spleen, or lymph nodes.[75,76]

At present, there is no indication that early treatment is able to affect the natural course of this lymphoma. Accordingly, the first-line management of asymptomatic patients consists of a watchful-waiting approach that allows sparing patients the risks of an untimely given therapy and to gather clinical data on symptoms and features that will guide decision-making about treatment.[7]

Actually, one notable exception is represented by patients presenting with HCV infection, who are candidates to receive upfront antiviral therapy with Pegilated Interferon-alpha and Ribavirin.[77,78] In up to 78% of HCV+ SMZL patients achieving clearance of HCV RNA following antiviral treatment, the sustained virological response has been reported to be paralleled by the clinical remission of the lymphoproliferative disease.[79,80]

For patients who present with or develop symptomatic cytopenias and/or abdominal discomfort, or other symptoms secondary to massive splenomegaly, splenectomy has been considered as the most effective approach producing a prompt relief of symptoms and a sustained recovery from cytopenia.[65,66] Following splenectomy, however, the disease persists in the BM and PB and eventually progresses in a median time of 4-5 years. For patients who progress after splenectomy, as well as for those who are unfit for splenectomy or unwilling to undergo surgery, systemic treatment may be appropriate.[72] However, when treatment should be started during the natural course of the disease, which patients would benefit most of such systemic therapy and which one would be the most effective drug combination, all remain open and debated issues. Moreover, no evidence of survival benefit in patients receiving a systemic therapy has been reported so far.

A good control over the disease, and even complete responses, can be achieved in naive (*i.e.*, not splenectomized) and relapsed patients through therapy with purine analogs fludarabine and pentostatine[81-83] while cladribine has been reported being non active administered by venous infusion for 7 days at dose of 0.1 mg/kg for one or two cycles. In another study,[84] cladribine was delivered at a dose of 5 mg/m^2 monthly for six cycles. In addition to cladribine, 32 out of 50 patients also received immunotherapy with the anti CD20 nonoclonal antibody rituximab, simultaneously or at the end of the induction

phase. The overall response rate was 87% and 15 of 24 cases (62%) who attained a CR also achieved a molecular remission. Interestingly, CR rate was 62.5% in the subgroup receiving rituximab *versus* 21.4% for cases treated with cladribine alone. Although this study was not designed to analyze subgroups and did not have the power to draw definite conclusions, it is tempting to speculate that immunotherapy with rituximab played a major role in achieving such a high CR rate.

Tsimberidou *et al.*[86] provided data suggesting superiority of rituximab or the association of rituximab with chemotherapy when compared with chemotherapy alone. In this retrospective study, rituximab containing therapeutic regimens resulted in longer overall survival and failure-free survival compared with chemotherapy. The ORRs were 88% with rituximab, 83% with rituximab plus chemotherapy, and 55% with chemotherapy alone; the 3-year survival rates were 95%, 100%, and 55%, respectively.

The high reported ORR (91-100%), the promptness in the resolution of splenomegaly, and sustained recovery from citopenia(s) without significant toxicity were remarkable findings and paved the way for the use of immunotherapy in SMZL.[87]

Moreover, preliminary results on rituximab as first-line monotherapy followed by a maintenance phase have been recently reported.[88] Fifty-eight SMZL patients were prospectively treated and rituximab was given in two phases: i) Induction phase, at a dose of 375 mg/m^2 per week for 6 weeks; ii) maintenance phase, at the same dose every 2 months for 1-2 years. The overall response rate (ORR) after the end of induction phase was 94% (CR 45%) and the median time to hematologic and clinical response was 4 and 5 weeks, respectively. Following completion of maintenance therapy (31 patients), 25 patients sustained their initial response, while 5 improved their response and 1 progressed. Interestingly, the 4-year PFS was significantly better (79% *vs.* 27% P=0.001), for patients who received maintenance. Overall, the above reported data suggest that immunotherapy with rituximab alone may be proposed as a reasonable therapeutic alternative to splenectomy.[86,87]

However, if immunotherapy or the addition of chemotherapy to rituximab may improve the clinical outcome or alter the natural course of the disease and which is the best schedule and dose of rituximab are burning and still unanswered questions. For selected patients who have undergone a histological transformation to a DLBCL or present a dissemination of the disease to nodal or extranodal sites, the adoption of anthracycline containing chemotherapies in addition to rituximab (R-CHOP or R-CHOP like) can be envisaged.[89] In this respect, the use of lyposomal doxorubicin seems attractive based on its peculiar pharmacocynetic profile, which allows the drug to reach concentration in the splenic tissue ten times higher than that of native doxorubicin.[90]

Diffuse red pulp splenic lymphoma and hairy cell leukemia variant

In spite of an extensive diagnostic work-up, including biomolecular, cytogenetic, and immunofenotypic investigations in addition to the histological examination of spleen and bone marrow, some cases of splenic lymphoma still lack diagnostic features that allow a precise categorization. In most instances, the clinical histopathological picture is that of a small B-cell lymphoproliferative disorder presenting as SML but which do not fall into any of the other well-recognized lymphoma entities described in the recent WHO classification and should be defined as SLs/leukemias unclassified.[9] The two best defined of these rare provisional entities are splenic diffuse red pulp small B-cell lymphoma (DRPSL) and hairy cell leukemia variant (HCL-v). DRPSL and HCL-V display very close biological and pathological features[10,91] and nearly all patients experience a clinical course quite similar to that of SMZL patient[92-93] Due to the rarity of these provisional entities, studies designed specifically to explore the therapeutic approach are lacking, then no therapeutic recommendation can be given. However, from the two largest retrospective series published so far, it appears that both HCL-v and DRPSL patients may benefit from splenectomy.[92-93] Moreover, HCL-v that despite its name is unrelated biologically to HCL, does not usually respond to interferon-alpha and rarely attains CR with purine analogues.[94-95] Interestingly, anecdotic reports have described two patients who attained a CR after treatment with Rituximab[94] suggesting that immunotherapy deserve to be investigated further in the treatment of patients with HCL-v or DRPSL.

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