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Non-MALT marginal zone lymphomas

C. Thieblemont[1]

[1]*Service d'hémato-oncologie, Hôpital Saint-Louis, Paris, France*

introduction

The concept of marginal zone B-cell lymphomas was developed in the 1990s for lymphomas whose cells originate from B lymphocytes normally present in a distinct anatomical location, the so-called 'marginal zone' (MZ). MZ has been described in the lymphoid organs—spleen and lymph nodes—and in non-lymphoid organs—mucosa-associated lymphoid tissue (MALT) or non-mucosal tissue such as skin, orbit and dura—as micro-anatomical sites situated around the mantle zone at the periphery of the splenic white pulp and at the periphery of lymphoid follicles. It was ascribed to the location of memory B cells at the end of the 1980s [1, 2]. Different entities of B-cell lymphomas are supposed to derive also from the cells of MZ. The International Lymphoma Study Group has individualized three distinct subtypes of MZL: (i) extranodal MZL of MALT type, (ii) splenic MZL (with or without villous lymphocytes) and (iii) nodal MZL (with or without monocytoid B cells) [3, 4]. In addition, entities with overlapping clinical, morphological and phenotypical features have been reported, including Waldenström macroglobulinemia/lymphophasmacytic lymphoma (WM/LPL) [5, 6], splenic red pulp lymphoma with villous lymphocytes [7] and hairy cell leukemia variant [8]. In spite of multifaceted phenotypic characterization, the absence of a clear consensus for diagnosis coming from the lack of typical markers and recurrent molecular abnormalities makes the identification of these entities difficult and are obstacles to conducting epidemiological surveys and to describing clinical features and outcomes, particularly for splenic MZL and nodal MZL. Moreover, few prospective studies on large series have been published to date, making therapeutic decisions difficult. Data regarding clinical and biological prognostic markers are limited, and it is therefore difficult to predict those in whom the disease will be more aggressive.

This review will present recent data describing the epidemiology, pathogenesis, clinical features, staging and therapy of non-MALT MZL.

epidemiology

MZL accounts for between 5% and 17% of all non-Hodgkin lymphomas (NHLs) in adults depending on the series. Splenic and nodal MZL represent 20% and 10% of MZLs, respectively, and account for <1% of NHL, MALT lymphoma being the most frequent of the MZL subtypes. Most of the cases of splenic and nodal MZL occur in adults, with a median age of ∼60 years, except for splenic MZL with villous lymphocytes (SLVL), which is occurring in adults at a median age of ∼70 years [9–17]. Sex ratio is variable according to the series. Growing evidence indicates that MZLs of MALT, splenic and nodal types are associated with chronic antigenic stimulation by autoantigens and/or microbial pathogens, inducing an accumulation of lymphoid tissue in the typical sites of involvement for each lymphoma entity in mucosa or organs that contain no native lymphoid tissue for MALT lymphomas, in spleen for splenic MZL and in nodes for nodal MZL. Splenic and nodal MZL have been described to be potentially associated with hepatitis C virus (HCV) infection particularly in northern Italy [18–20] compared with other countries [21].

splenic MZL

clinical features of splenic MZL

Splenic MZL is rare and overlaps with other indolent lymphomas. The hallmark of the clinical presentation is usually splenomegaly [9, 10, 22]. The splenomegaly becomes symptomatic when massive and/or associated with cytopenias. Early in the disease, however, splenomegaly may be detectable only on computed tomography (CT) scanning. Small involved splenic hilar lymph nodes are frequently present. Peripheral lymph node involvement is unusual [4]; if it is present, the presentation is usually classified as a disseminated nodal and splenic subtype [11]. Bone marrow infiltration is almost constant (83–100% of the cases), while blood involvement is variable, between 29% and 75% of the cases [14, 15, 22, 23]. Whereas the serum lactate dehydrogenase (LDH) level is usually normal in splenic MZL, the β2-microglobulin level is increased. A large proportion of patients have a serum monoclonal paraprotein (M-component), mainly of the μ (IgM) isotype and generally <20 g/l [22]. In some patients, the first manifestation of the lymphoma is an immune hemolytic anemia (7–16%) or an immune thrombocytopenia (2–5%). These patients may respond to corticosteroids. Uncommonly, autoantibodies against coagulation factors are present. Splenic MZL associated with HCV infection has been described, particularly in northern Italy [18]. HCV-associated splenic MZL is indistinguishable from classic splenic MZL, except for the presence of HCV viral replication and coexistence of liver disease [24].

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diagnostic procedures and positive diagnosis

Patients with splenic MZL often present with lymphocytosis, cytopenias or symptomatic splenomegaly. Bone marrow examination shows an involvement in most of the cases. The morphology of these cells usually suggest the diagnosis of splenic MZL [25]. In 15% of the cases, blood involvement is represented by villous lymphocytes, lymphocytes displaying cytoplasmic protrusions [22]. It is controversial whether SLVL is the leukemic counterpart of all splenic MZLs or whether it is a subentity of splenic MZL. Recently, a variant of splenic MZL has been characterized with villous lymphocytes harboring morphologic and molecular particularities similar to Hairy cell variants [7]. Immunophenotyping is essential to eliminate the characteristic phenotypes of other types of small B cell lymphoma, but the lack of typical markers represents a handicap for difficult cases. Cytogenetic studies reporting the presence of characteristic cytogenetic abnormalities such as 7q deletion may confirm this, but the absence of recurrent translocation. Similarly molecular data showed a biased used of VH1-2 immunoglobulin variable gene segment but also genetic heterogeneity. Recently, genomic instability, gene expression profiling and microRNA analyses have demonstrated unique profiles for splenic MZL compared with other B-cell lymphomas suggesting a specific pathogenesis and potential new markers [26–30]. In rare cases, when the blood and bone marrow are not involved, the diagnosis can only be made after splenectomy.

treatment

Patients with moderate asymptomatic splenomegaly may be followed without any treatment [9, 10, 22, 31]. The absence of treatment does not influence the course of the disease and these patients often have stable disease for at least 10 years [10, 32]. When treatment is indicated (i. e. occurrence of a large symptomatic splenomegaly and/or cytopenia), splenectomy is the treatment of choice [22]. Splenectomy is beneficial in terms of improvement of performance status and correction of cytopenias [9, 22]. This benefit, which is due to the disappearance of hypersplenism but also the reduction of marrow infiltration after splenectomy [33], persists for years, with an interval before requiring further treatment of >5 years, even if the patient develops progressive lymphocytosis [22]. Chemotherapy based on alkylating agents (chlorambucil or cyclophosphamide) or purine analogs (fludarabine) has also been reported as an effective treatment in non-randomized studies or in retrospective analyses [22, 34]. The role of adjuvant chemotherapy in the setting of adverse prognostic factors [16] such as high LDH level, anemia or hypoalbuminemia and/or presence of B symptoms, or because of the presence of large cells (>20%) has not been established. Although chemotherapy may increase the number of complete responses, it has no impact on the risk of relapse, histological progression or survival in comparison with patients who receive no adjuvant chemotherapy [22]. Chemotherapy alone may be proposed initially to patients with contraindications to surgery but who require treatment or later for patients with clinical progression after splenectomy. In this setting, good responses have been reported with single-agent fludarabine but not with 2-deoxycoformycin [35]. Good responses have been observed with rituximab alone or associated with chemotherapy. And recently the benefit of polychemotherapy based on non-pegylated lyposomal doxorubicin after splenectomy or not has been reported to be under evaluation in the GISL [36]. In cases of HCV-associated splenic MZL, antiviral treatment with interferon (IFN)-α or IFN-α plus ribavirin has been reported in a small series to be associated with a marked reduction of lymphocytosis and splenomegaly, whereas antiviral therapy is ineffective in HCV-negative splenic MZL [24]. This very interesting observation warrants further follow-up.

outcome and prognostic factors

Patients with splenic MZL have a long survival in most reported series, with >50% survival at 5 years [9, 10, 22, 31]. Progression to lymph nodes or extranodal sites may occur, described with a median time to progression of 3.7 years [22]. Histological transformation to diffuse large B cell lymphoma (DLBCL) is rare, occurring at the time of tumor recurrence in 10–20% of patients, and is clinically associated with B symptoms, poor performance status, disseminated disease in nodal and extra-nodal locations, high LDH and poor outcome (median survival of 26 months [22]). Transformation may occur at diagnosis (seen on the removed spleen) or at time of progression with a median time to transformation of 12–85 months [22, 37]. Transformation is frequently associated with p53 inactivation or new chromosomal abnormalities. In our experience the International Prognostic Index (IPI) often used for lymphomas can not discriminate patients because none of the IPI criteria (age, performance status, stage, number of extranodal sites and LDH level) influences outcome [22]. Conversely high LDH level and IPI have been reported to be related to worse prognostic [16]. Leukocyte count >30 or >20 × 10^9/l, lymphocytes <4 or >20 × 10^9/l, high β2-microglobulin level, presence of monoclonal component, anemia, hypoalbuminemia and initial treatment with chemotherapy have been described as adverse prognostic factors [10, 22, 31].

nodal MZL with or without monocytoid B cells

clinical presentation

Because of the more recent identification of this lymphoma, clinical data restricted to nodal MZL may be found in few reports in the literature [13, 38–41], with limited numbers of patients (21, 22, 36 and 47 patients, respectively). The median age for these patients is 50–62 years, with a slight male predominance. The vast majority of the patients present with disseminated peripheral, mostly cervical, and abdominal nodal involvement. Bone marrow involvement occurred in less than half of the patients (28%, 43% and 44%, respectively) [12, 13, 39]. Peripheral blood involvement is very rare. There is no difference between these groups with respect to B symptoms, elevated LDH, performance status or IPI score compared with other primary nodal B-cell lymphomas such as follicular lymphomas [12]. Elevated β2-microglobulin is found in one-third of the patients, and an M-component is infrequently

detected (8%) [42]. Cytopenias are rare [39], and few cases are reported to be associated with HCV [39].

diagnostic procedures

The morphological and phenotypical description is still incomplete in the literature. Cytogenetic data could help but remain sparsely reported [43–45].

outcome and prognostic factors

The outcome of patients with nodal MZL is similar to that of patients with splenic MZL but worse than that of patients with MALT lymphoma. Estimated 5-year overall survival is reported as between 50% and 70% [12, 13], without any plateau, suggesting that the disease is not currently curable. The estimated median time to progression is between 1 and 2 years [12, 42]. This may be explained by the fact that 20% of patients present at diagnosis with a component of large cells (>20%) and a high mitotic count with evidence of transformation into DLBCL [12]. Given the small numbers of cases reported, no specific prognostic factors are proposed. At the time of relapse, nodal involvement is usually predominant, although splenic or extranodal involvement may occur.

treatment

A precise recommendation for therapy is difficult because of the limited data available. The disease is characterized as having good survival but a short time to progression, and logical treatment options include polychemotherapy, with or without anthracyline, associated with rituximab [46].

conclusion

Although the World Health Organization lymphoma classification has provided significant advances in defining non-MALT MZL, several issues regarding the pathogenesis and clinical course of these lymphomas remain to be defined. Collaboration of clinicians and pathologists in defining stringent diagnostic criteria will help in designing prospective clinical trials to define the optimal therapeutic approach to these diseases.

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