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Marginal zone lymphomas: Reconsidering similarities and differences while moving towards personalized treatment

Emanuele Zucca [a, *], Aaron Polliack [b], Franco Cavalli [a]

[a] Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland
[b] Hadassah University Hospital and Hebrew University Medical School, Jerusalem, Israel

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A B S T R A C T

Knowledge on marginal zone lymphomas (MZL) has expanded since the first description of Mucosa-Associated Lymphoid Tissue (MALT) lymphomas in 1983. It later became evident that similar lymphomas could arise in a variety of different extranodal organs and that similar histological features were present in a group of primary lymphomas arising in the spleen and in the lymph nodes. The World Health Organization (WHO) Classification of Tumors of Haematopoietic and Lymphoid Tissues considered, for the first time in 2001, nodal, extranodal (MALT) and splenic MZL as independent mature neoplasms derived from B cells normally present in the marginal zone. This concept has been maintained across the 2008 classification, as well as in the recent 2016 revision. In the latter, the concept of clonal B-cell lymphocytosis with features consistent with marginal zone origin, possibly a precursor of splenic MZL, was also introduced. Chronic antigenic stimulation of either infectious or autoimmune origin is a proven major pathogenetic event. Several molecular aberrations have been described in the three MZL subtypes. Remarkably, MALT lymphoma carries recurrent chromosomal translocations, with at least three of them affecting the nuclear factor kB (NF-kB) pathway. Recurrent mutations affecting the Notch pathway have also been described in both nodal and splenic MZL. In summary, a spectrum of MZL can arise at different sites and evidence is emerging that different pathogenetic mechanisms may contribute to different outcomes. These differences make MZL a challenging group of entities that still require further study.

Knowledge on marginal zone lymphomas (MZL) has expanded exceptionally since the first description of Mucosa-Associated Lymphoid Tissue (MALT) lymphomas reported in 1983 by the British pathologists Isaacson and Wright. Their paper in *Cancer* was the first attempt to consider a group of extranodal indolent lymphomas arising from this tissue as a separate entity. Their observation was made after biopsies from a case of intestinal “Mediterranean lymphoma” with alpha heavy chain disease (an entity currently defined as Immunoproliferative small intestinal disease, IPSID) from a Middle Eastern patient and a case of indolent gastric lymphoma from a British patient were placed under their microscope on the same day and examined. They noted that these lymphomas shared similar features and histologically mimicked the architecture of Peyer patches far more than lymphomas of peripheral lymph nodes [1].

* Corresponding author. Oncology Institute of Southern Switzerland, Ospedale San Giovanni, 6500, Bellinzona, Switzerland. Fax: +41 91 811 9182.
E-mail address: ielsg@eoc.ch (E. Zucca).

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Two types of MALT can clearly be distinguished, a native type constituted by lymphoid tissue physiologically present in the gut (such as the Peyer patches), whereas acquired MALT appears to develop in sites of inflammation in response to either infectious or autoimmune processes. Nowadays it is accepted that in the context of these prolonged lymphoid reactive proliferations, the development and subsequent growth of a pathological clone can progressively replace the normal lymphoid population, giving rise to a MALT lymphoma [2].

After the first report by Isaacson and Wright [1], it soon became evident that similar lymphomas could arise in a variety of different extranodal organs, including thyroid, salivary glands and lung. This led to the proposal that there is a wider group of extranodal B-cell lymphomas with a common origin from MALT. Before the recognition of this entity, many of these diseases were diagnosed as "pseudolymphoma", in the light of the very indolent behavior of this group of disorders compared to nodal lymphomas. The term "pseudolymphoma" was later rejected when their neoplastic nature was clarified [3]. Very similar histological features were also described in a group of primary lymphomas arising from the marginal zone of the spleen [4–6] and in lymph nodes affected by what was then termed, monocytoid B cell lymphoma [7].

In 1994, the first official lymphoma classification uniting the American and the European school of thought was published in Blood (REAL classification). Within the broad group of "*peripheral B-cell neoplasms*" there was one definite entity, extranodal MZL (MALT-type ± monocytoid B cells). The nodal MZL (± monocytoid B cells) was kept as a provisional subtype in this category while splenic MZL (± villous lymphocytes) was kept as a provisional entity [8].

The first World Health Organization (WHO) Classification of Tumors was published in 2001 [9] and for the first time nodal, extranodal (MALT) and splenic MZL were considered as independent mature B-cell neoplasms. This concept has been maintained across the 2008 classification [10–12] as well as in the recent 2016 edition [13]. In the latter, the concept of clonal B-cell lymphocytosis with features consistent with marginal zone origin, possibly a precursor of splenic MZL, was also introduced [14]. We now recognize three specific and separate neoplastic entities which are much better understood than when first reported. IPSID is also included in the WHO classification as a special subtype of MALT lymphoma, which was quite prevalent in the Middle East. MALT lymphoma constitutes approximately 8% of all non-Hodgkin lymphoma [15] while splenic and nodal MZLs are not as frequent, each comprising about 1% of lymphoid neoplasms [15].

These neoplasms derive from B cells normally present in the marginal zone which is the more external layer of the B lymphocyte follicle surrounding the follicle center and the mantle zone. Physiologically, this area is wider in organs with a high antigen flow, such as the spleen, mesenteric lymph nodes and the Peyer patches. The most common cells in the marginal zone are naïve B cells with a restricted immunoglobulin repertoire, which implies, those involved in a T cell independent early immune response. However center memory B cells, plasma cells, macrophages and T cells are also post-germinal. In MZL, the neoplastic infiltrate invades the marginal zone and extends into the interfollicular regions, sparing the non-neoplastic, reactive, follicles. In epithelial tissue a frequent impressive finding is the invasion of this epithelium, forming the so-called lymphoepithelial lesions which can eventually lead to destruction of the crypt epithelium. The B cell tumor infiltrate is mainly composed of centrocyte-like cells, with abundant pale cytoplasm and irregular shaped nuclei. There are also some cases where the tumor cells resemble monocytoid cells or small lymphocytes and scattered transformed immunoblast- or centroblast-like cells can also be present. If these large cells form solid sheets, a diagnosis of diffuse large B-cell lymphoma should then be made, but making note of the accompanying presence of MALT lymphoma. The old term "high-grade MALT lymphoma", as distinct from "low-grade MALT" lymphoma, is considered incorrect today, and it has been suggested not to use this anymore [10]. Plasma cell differentiation can be present in up to one third of the cases, being sometimes so pronounced that a differential diagnosis with plasmacytoma must be ruled out [15].

MALT lymphomas usually remain confined to the site of origin at diagnosis, very rarely invading the bone marrow, but this may occur late in the course of the disease. This phenomenon of early stage at presentation is considered to be linked to the intrinsic homing properties of these lymphocytes, which are very different from those in lymph nodes. It has been hypothesized that a common pool of lymphocytes migrates between different mucosal systems rather than via the peripheral lymph nodes [15]. In contrast with this presentation, splenic MZL regularly involves the bone marrow and may also be found in the peripheral blood as circulating "villous lymphocytes", but rarely infiltrate peripheral lymph nodes and extranodal tissue [16]. In contrast nodal MZL is typically found in peripheral lymph nodes and only occasionally involve the bone marrow and peripheral blood [17]. A presentation with concomitant extranodal, nodal, and/or splenic involvement, is not uncommon in patients with advanced disease making the differential diagnosis of the different MZL entities not that straightforward always [18,19].

A differential diagnosis of marginal zone lymphomas with other small B-cell lymphomas, such as mantle cell lymphoma, follicular lymphoma and small lymphocytic lymphoma is based on immunohistochemistry, together with genetic studies (classic or molecular). In this regard there is no pathognomonic finding for marginal zone lymphomas and a variety of molecular aberrations have been described. In particular, the genetic relation between the different MZL entities still remains unclear, despite the many karyotype and molecular aberrations described over the years [20]. A comprehensive analysis of genomic DNA copy number changes in a very large series of more than 200 cases of MZL showed that the three MZL subtypes share some common genetic abnormalities but also carry subtype-specific lesions, which may have an impact on the clinical outcome. MALT lymphoma presented significantly more frequently gains at 3p, 6p, 18p, and del(6q23), while splenic MZL was associated with del(7q31), del(8p). Compared to MALT lymphoma nodal MZL lymphoma did not appear statistically different, but they do appear to be lacking the splenic MZL-related 7q losses. Gains of 3q and 18q were common to all 3 subtypes [21].

Unlike the other two MZL types, MALT lymphoma carries recurrent chromosomal translocations, with at least three of them affecting the nuclear factor kB (NF-kB) pathway. These can also be constitutively activated by the inactivation of

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