Seminars in Cancer Biology 24 (2014) 33–42

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Chronic inflammation and extra-nodal marginal-zone lymphomas of MALT-type

Catherine Thieblemont[a,1], Francesco Bertoni[b,1], Christiane Copie-Bergman[c], Andrés J.M. Ferreri[d,e], Maurilio Ponzoni[e,f,*]

[a] APHP-Hôpital Saint-Louis, Department of Hemato-oncology, Paris Diderot 7 University, INSERM U728, Paris, France
[b] IOR Institute of Oncology Research, Lymphoma and Genomics Research Program, and Oncology Institute of Southern Switzerland, Lymphoma Unit, Bellinzona, Switzerland
[c] APHP-Hôpital H. Mondor, Department of Pathology, Creteil, France
[d] San Raffaele Scientific Institute, Department of Onco-Hematology, Milano, Italy
[e] San Raffaele Scientific Institute, Unit of Lymphoid Malignancies, Milano, Italy
[f] San Raffaele Scientific Institute, Pathology Unit, Milano, Italy

ARTICLE INFO

Keywords:
MALT lymphoma
Chronic inflammation
Marginal zone
Microbial pathogen autoimmune disease

ABSTRACT

Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT) is an indolent B-cell non-Hodgkin lymphoma (NHL) arising in lymphoid populations that are induced by chronic inflammation in extra nodal sites. The stomach is the most commonly affected organ, and MALT lymphoma is clearly associated with a gastroduodenitis induced by a microbial pathogen, *Helicobacter pylori*, thus gastric MALT lymphoma represents a paradigm for evaluating inflammatory-associated lymphomagenesis. Variable levels of evidence have indicated a possible association between other microorganisms and non-gastric MALT lymphomas. In addition to infectious etiology, chronic inflammation arising as a result of autoimmune diseases such as Sjogren's syndrome or Hashimoto thyroiditis, poses a significant risk factor for developing NHL. Recently, genetic alterations affecting the NF-κB pathway, a major signaling pathway involved in many cancers, have been identified in MALT lymphoma. This review will present MALT lymphoma as an example of the close pathogenetic link between chronic microenvironmental inflammation and tumor development, showing how these observations can be integrated into daily clinical practice, also in terms of therapeutic implications, with particular focus on the NF-κB pathway.

1. Introduction

The marginal zone of B-cell follicles is especially well developed in lymphoid organs that are continuously exposed to antigenic stimulation [1]. The marginal zone is easily observed in the spleen and to a lesser extent, in mucosa-associated lymphoid tissues (MALT), whereas it is scarcely identifiable in lymph nodes [1]. In the spleen, the marginal zone has a crucial role in T-cell-independent responses to various antigens, including polysaccharides derived from encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitides*, and *Haemophilus infuenzae* [1]. In addition, marginal zone B-cells are *per se* primed for involvement in the immune response, since they are a source of natural antibodies (mostly IgM), which are available even in the absence of antigenic challenge and show polyreactivity against self and exogenous antigens [1,2].

Lymphomas arising from the marginal zone, termed marginal zone lymphomas (MZL), account for 5–17% of all non-Hodgkin lymphomas [3]. According to the sites involved, three subtypes of MZL are distinguished in the last WHO classification: (1) the extra nodal marginal zone of mucosa-associated lymphoid tissue or MALT lymphoma; (2) the splenic MZL (SMZL); (3) and the nodal MZL [4].

MALT lymphoma differs from SMZL and nodal MZL as it arises in organs that normally lack lymphoid tissue, such as the stomach, lung, ocular adnexa, or salivary glands, but accumulate B-cells in response to chronic inflammation. This chronic inflammation may be due to either chronic infection or autoimmune processes [5]. Sustained antigenic or auto antigenic stimulation not only triggers polyclonal B-cell proliferation, but also recruits a series of inflammatory cells, including T-lymphocytes, macrophages and neutrophils, to the site of inflammation. Additional microenvironmental components, such as endothelia, contribute to the pathogenesis of these lymphomas as well. The inflammatory components may promote the growth of neoplastic B-lymphocytes by either one of two mechanisms: (i) a direct one, where, for instance,

* Corresponding author at: Pathology Unit, Ospedale San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milano, Italy. Tel.: +39 0226432544; fax: +39 0226437070.
E-mail address: ponzoni.maurilio@hsr.it (M. Ponzoni).
[1] Both authors contributed equally.

1044-579X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.semcancer.2013.11.005

neutrophils release reactive oxygen species (ROS), which cause a wide range of genetic aberrations [6]; (ii) an indirect one, where chronic inflammation sustains and prolongs proliferation of B-cells, with the consequent increased risk of double-stranded DNA breaks and translocations, owing to the inherent genetic instability of B-cells during somatic hypermutation and class-switching recombination [7]. Several genetic aberrations have been identified in MALT lymphomas, such as trisomy of chromosomes 3 and 18, and characteristic, mostly exclusive, translocations. Many of these recurrent chromosomal translocations and unbalanced genomic aberrations disrupt genes and related protein products involved in multiple and diverse levels of the nuclear factor κB (NF-κB) pathway [8]. The constitutive activation of NF-κB may therefore result in uncontrolled B-cell proliferation that eventually favors the development of overt lymphoma [9].

The present review aims to link the available data on the intrinsic properties of MZL B-cells to the mechanisms orchestrated by the microenvironmental inflammatory milieu, which in turn may substantially contribute to the development of these lymphomas.

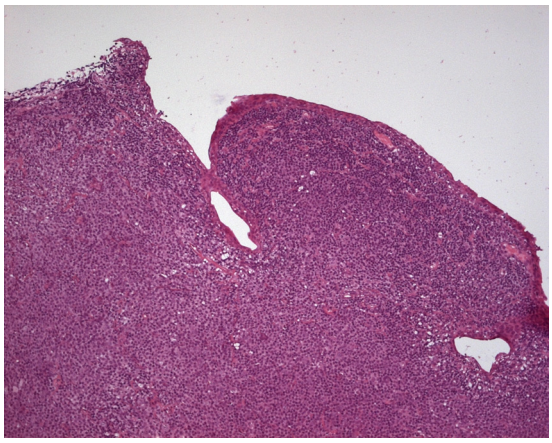

Fig. 1. A case of conjunctival marginal zone B-cell lymphoma showing replacement of lamina propria by dense infiltrate made by medium-sized lymphocytes (Hematoxylin–Eosin, 100×, original magnification).

2. Epidemiological links between various microorganisms and anatomical sites in MALT lymphomas

The best-studied association involves *Helicobacter pylori* (*Hp*) and gastric MALT with a prevalence of the bacterium in up to 90% of cases [10]. The second most studied association is *Chlamydophila psittaci* (*Cp*) in ocular adnexal lymphomas (OAL), which exhibits geographic variability: the prevalence of *Cp* in OAL ranges from 47% to 80% in Italy, Austria, Germany and Korea, while the percentages are much lower in other countries, including the United States [10]. A similar geographical variation is observed for the association between *Borrelia burdgorferi* (Bb) and cutaneous MALT lymphoma. Although generally less frequent, this association varies between 10 and 42% in Europe [10], and is almost absent in non-endemic areas [11]. Finally, less robust data support the association between *Campylobacter jejuni* infection and Immunoproliferative small intestinal disease, due to the low frequency of reported cases and the modest levels of evidence [10].

2.1. Autoimmunity and MALT lymphomas

Patients with Sjogren Syndrome (SS) display a 1000-fold increased risk of developing a MALT lymphoma of the parotid gland. In addition, the risk of developing MALT lymphoma increases by 2.7-fold in Systemic Lupus Erythematous [12]. From a pathogenetic standpoint, it has been hypothesized that, in the case of SS, a local chronic antigen-driving stimulation triggers the development of organized lymphoid tissue. In this context, the overexpression of B-cell activating factor (BAFF) leads to excessive immunoglobulin production and reduced apoptosis, providing a stimulus for sustained proliferation of B-cells, which eventually become autoantibody-producing plasma cells [13].

2.2. Pathological features of extra nodal marginal zone lymphomas

In most instances, these lymphomas are often multifocal, with small, often microscopic clonally identical foci of lymphoma scattered throughout the involved organ [14]. MALT lymphoma is composed of heterogeneous B-cells, including medium-sized centrocytic-like cells, small lymphocytes with round nuclei and clumped chromatin, and monocytoid cells (Fig. 1). One or more cytological features can predominate, or the different types of cells can coexist to various degrees within the same case. In some cases, plasma cell differentiation may occur and shares with the lymphocytic component the same light chain restriction by immunohistochemistry. Scattered and rare (usually less than 15–20%) large cells (immunoblastic- and centroblastic-like) may occur within the lymphoid population. Very rarely blast cells form solid or sheet-like proliferations; in such instances, a separate diagnosis of a diffuse large B-cell lymphoma should be made [15]. Neoplastic B-cells can infiltrate and disrupt the mucosal crypts and glands, forming lymphoepithelial lesions, although these structures are not pathognomonic and diagnostic for MALT lymphoma, since they can also occur in some reactive conditions [16] and in other lymphoma subtypes. Along with lymphomatous cells, reactive T lymphocytes [15] (Fig. 2), neutrophils, monocytes/macrophages, and vessels (Fig. 3) can be recognized. Histopathological examination remains the gold standard for diagnosis and the detection of monoclonality by polymerase chain reaction (PCR) represents a useful aid, keeping into mind that it can be observed in benign inflammations, such as chronic gastritis [17], and conversely, cannot be detected in up to 15% of cases of overt MALT lymphomas [18].

The tumor cells typically express IgM, less often IgA or IgG; they are positive for CD20, CD79a, CD21, and CD35, and they are negative for CD5, CD23, CD10, and cyclinD1, recapitulating the immunophenotype of normal marginal zone B-cells. These data show that, until recently, there were not specific immunohistochemical markers for MALT lymphoma. However, two interesting molecules have been recently reported: myeloid cell nuclear differentiation

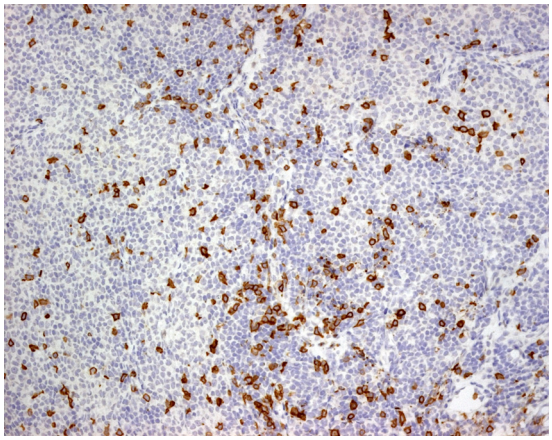

Fig. 2. Neoplastic lymphocytes are infiltrated by a variable amount of reactive T-cells (CD3, 200×, original magnification).