Novel developments in the pathogenesis and diagnosis of extranodal marginal zone lymphoma

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Abstract Extranodal marginal zone lymphoma (EMZL), mostly represented by mucosa-associated lymphoid tissue (MALT) type, also referred to as MALT lymphoma, is a clinically heterogeneous entity within the group of low-grade B cell lymphomas that arises in a wide range of different extranodal sites, including the stomach, lung, ocular adnexa, and skin. It represents the third most common non-Hodgkin lymphoma in the Western world, and the median age of occurrence is around 60 years. One characteristic aspect in a subset of EMZL detectable in about 25% of the cases is the presence of specific chromosomal translocations involving the genes *MALT1* and *BCL10*, which lead to activation of the NF-κB signaling pathway. Another unique aspect is that several infectious agents, such as *Helicobacter pylori* in the case of gastric EMZL, and autoimmune disorders, like Sjögren syndrome, have been implicated in the pathogenesis of this cancer. Recent findings as summarized in this review have further improved our understanding of the complex pathobiology of this disease and have been essential to better define novel treatment strategies. In addition, many of these specific features are currently being implemented for the diagnosis of EMZL.

Keywords Lymphoid malignancies · Chromosomal rearrangements · Infections · MALT · EMZL

Introduction

There are three different types of marginal zone lymphomas (MZLs): (i) extranodal marginal zone lymphoma (EMZL), mostly represented of mucosa-associated lymphoid tissue (MALT) type; (ii) splenic MZL (SMZL); and (iii) nodal MZL (NMZL). EMZL accounts for about 7% of all adult non-Hodgkin lymphoma (NHL) and 70% of MZL [1]. The most predominant site for EMZL involves the stomach (70%), but virtually all other organs can be affected, including the lung, salivary gland, ocular adnexa, skin, and thyroid. Despite their clinical heterogeneous presentation, at least three common variants of chromosomal translocations have been identified as specific for EMZL, all of which affect the NF-κB pathway [2]. Moreover, EMZLs are frequently associated with chronic inflammation and infectious agents that give rise to chronic infections, such as *Helicobacter pylori* in gastric EMZL, *Chlamydia psittaci* in ocular adnexa EMZL, *Campylobacter jejuni* in cutaneous EMZL [3]. On the other hand, several autoimmune disorders, including Sjögren syndrome, lymphoepithelial sialadenitis and Hashimoto thyroiditis, predispose to EMZL development. The prevailing view is that continuous immune stimulation resulting from chronic infections and autoimmune inflammatory diseases cooperates with recurrent genetic aberrations resulting in lymphoid transformation.

EMZL, in general, shows a remarkably indolent disease course with a median survival of more than 12 years [4]. However, in a small proportion of cases, EMZL can progress and undergo histological transformation into aggressive high-grade tumors, mostly diffuse large B cell lymphoma (DLBCL) [5]. A common feature of EMZL is deregulation of the proteolytic activity of the MALT1 protein, which results in constitutive nuclear factor κB (NF-κB) stimulation. Current and...
novel therapeutic strategies are aimed to target these specific features underlying the molecular pathogenesis of EMZL. In this review, novel insight into molecular pathogenesis of EMZL will be described and its impact on diagnosis and therapy of this disease spectrum.

**Clinical features of EMZL**

EMZL often occurs in organs devoid of prominent organized lymphoid tissue, where as a result of chronic inflammation, outgrowth of a malignant clone progressively replaces the reactive lymphocyte population. Irrespective of the site of origin, EMZL is characterized by an indolent presentation and course, mainly occurring in adults with a median age of 60 years. The clinical presentation differs depending on the organ involved. Patients with gastric EMZL often present with symptoms that mimic those of peptic ulcer disease or gastritis (nausea, dyspepsia, and chronic fatigue), while recurrent respiratory infections, chest pain, and dyspnea are observed in patients with pulmonary EMZL. Patients with conjunctival EMZL may present with blury vision or other visual field defects. The majority of the patients with EMZL display localized stage I or II extranodal disease (Ann Arbor staging system), involving epithelial tissues at specific sites, including the gastrointestinal tract. In about 30% of the cases, these lymphomas disseminate to other MALT sites, predominantly lymph nodes and in very rare cases to the bone marrow, but the peripheral blood is usually not involved [6]. The outcome of patients with EMZL is good with a 5-year overall survival between 86 and 95%, without any significant differences between the site of the EMZL, localized or disseminated disease [7].

**Pathogenesis of EMZL**

The term “marginal zone lymphoma” refers to the fact that these lymphoma cells are derived from post-germinal center memory B cells normally present in the marginal zone of lymphoid organs. In nearly all cases, EMZL displays fully rearranged immunoglobulin heavy chain variable (IGHV) and light chain genes, which show somatic hypermutation and class switching [8, 9]. In many cases, EMZL has been shown to be associated with chronic immune reactions driven by bacterial, viral, or autoimmune stimuli (Table 1). This latter aspect correlates with the observation that patients with autoimmune disorders harbor an increased risk for the development of lymphomas [10, 11]. These findings have led to the hypothesis that this type of indolent lymphoma follows a multistage development that starts with an infection combined with (auto-)antigenic stimulation or other direct effects on B cells, like the presence of free radicals in an inflammatory surrounding. With the subsequent accumulation of genetic alterations, which frequently result in activation of the NF-κB pathway, neoplastic transformation can occur, decreasing the dependency of antigenic stimulation (Fig. 1). Nonetheless, many of the EMZL show regression upon eradication of the bacterial infections with specific antibiotic treatment, which is mainly the case in translocation-negative EMZL.

**Bacterial infections**

*Helicobacter pylori* *H. pylori* infection is present in 85–90% of gastric EMZL, and support for its role as an etiologic factor was provided in the early 1990s after demonstration of tumor regression in the early-stage cases treated with antibiotic therapy. Although *H. pylori* infection can be detected in about 50% of the general population giving rise to chronic active gastritis or even peptic ulcer disease, only ~1% of the infected subjects will develop gastric adenocarcinoma or lymphoma. A population-based study has demonstrated a declined incidence of gastric EMZL after specific intervention for *H. pylori* infections in patients with acid peptic disease symptoms [12].

More direct support for the role of *H. pylori* in the pathogenesis of gastric EMZL derives from studies that have shown that gastric EMZL cell growth could be stimulated in culture by *H. pylori*-specific T cells [13]. An additional effect of *H. pylori* on the microenvironment is the release of the proliferation-inducing ligand (APRIL) by lymphoma-associated macrophages [14]. Furthermore, the *H. pylori* cytotoxin-associated gene A (CagA) protein has direct oncogenic properties both for gastric epithelial cells and B lymphocytes [15, 16]. The CagA protein can enter B cells via type IV secretion system in an ATP-dependent manner [17], where it undergoes tyrosine phosphorylation by SRC or ABL kinases in the C-terminal region [18, 19]. Phosphorylated CagA interacts with Grb2 and tyrosine phosphatase SHP-2 leading to ERK activation [20], which promotes phosphorylation of the pro-apoptotic protein BAD and upregulation of the anti-apoptotic molecules BCL2 and BCL-X[17, 21]. Detection of CagA, phospho-SHP2, and phospho-ERK predicts involvement and dependence of *H. pylori* in the pathogenesis of gastric EMZL [22]. Alternatively, CagA can block cell cycle progression and inhibits B lymphocyte apoptosis by impairing the JAK/STAT and p53 pathway [23, 24]. Furthermore, *H. pylori* activates the NF-κB pathway in lymphocytes through both the canonical and non-canonical pathways [25]. These findings provide further evidence that gastric EMZL follows a multistage progression from chronic gastritis to gastric lymphoma that starts with *H. pylori* infection.

*Helicobacter heilmannii* Additional non-*H. pylori* species have been identified in human gastric mucosa, now reclassified as *Helicobacter heilmannii* sensu lato (*H. heilmannii* s.l.) without specific sequence information;
and *Helicobacter heilmannii* sensu stricto (*H. heilmannii* s.s.) or any of the other ten species names if definite identification at the species level is achieved [26]. The frequency of human *H. heilmannii* s.l. infection is less than 1% of the population in industrialized countries and 3–8% in developing countries. Similar to *H. pylori*, *H. heilmannii* s.l. infection has been associated with gastritis, peptic ulcer disease, gastric carcinoma, and gastric EMZL [27]. However, it seems that there is a relatively higher prevalence of gastric EMZL in patients with *H. heilmannii* s.l. gastritis, i.e., 2% in comparison to 0.7% among patients with *H. pylori* gastritis [28].

**Chlamydophila psittaci** The *Chlamydophila* genus is the etiologic agent of psittacosis, also known as parrot disease, an infection caused by exposure to infected bird species. *C. psittaci* was recognized as a potential trigger of ocular adnexal lymphoma, when Ferreri et al. showed the efficacy of antibiotic treatment [29, 30]. *C. psittaci* DNA has been detected in a variable percentage of ocular adnexal lymphoma, with a high incidence of 47 to 80% in especially Italy, Austria, Germany, and Korea, but with a much lower incidence in UK and Southern China [31], while there was no evidence of *C. psittaci* infection in cases from the USA and Japan [32–34]. However, support for its role as a causative agent in ocular adnexal lymphoma has been provided by the findings of detecting chlamydial antigens in tumor biopsies and the isolation of chlamydia from conjunctival swabs and peripheral blood from lymphoma patients as well as the visualization of *C. psittaci* within tumor-infiltrating macrophages by electronic microscopy [35].

**Campylobacter jejuni** The Gram-negative helical-shaped *Campylobacter jejuni*, which is usually carried by birds, represents one of the most common causes of gastroenteritis in the world. Persistent infection leads to severe gastrointestinal illness, which requires antimicrobial therapy, including macrolides and fluoroquinolones. *C. jejuni* is also an initiating factor in chronic autoimmune disease, such as Guillain-Barré syndrome and reactive arthritis [36]. *C. jejuni* has also been associated with the pathogenesis of immunoproliferative small intestinal disease (IPSID), a special subtype of EMZL that primarily occurs in young adults of the Middle East, North and South Africa, and the Far East. The presence of *C. jejuni* DNA has been demonstrated in a small cohort of IPSID samples [37], and clinical response to antibiotics directed at this infection has been described in a single study [38].

| Primary site       | % EMZL | Infection/autoimmunity | Genetic alterations |
|--------------------|--------|-------------------------|---------------------|
| Stomach            | 70     | *Helicobacter pylori* (85%)<br>*Helicobacter heilmannii* (< 1%) | t(11;18)(q21;q21)/BIRC3-MALT1 (23%)<br>t(3;14)(p14;q32)/IGH-FOXP1 (3%)<br>t(1;14)(p22;q32)/IGH-BCL10 (2%)<br>t(14;18)(q32;q21)/IGH-MALT1 (1%)<br>TNFαP3 inactivation (5%) |
| Salivary gland     | 9      | Lymphoepithelial sialadenitis/ Sjögren syndrome (20–45%)<br>Hepatitis C virus (30%) | t(14;18)(q32;q21)/IGH-MALT1 (6%)<br>t(11;18)(q21;q21)/BIRC3-MALT1 (2%)<br>t(1;14)(p22;q32)/IGH-BCL10 (1%)<br>TNFαP3 inactivation (8%) |
| Ocular adnexa      | 7      | *Chlamydophila psittaci* (10–50%) | t(3;14)(p14;q32)/IGH-FOXP1 (20%)<br>t(14;18)(q32;q21)/IGH-MALT1 (16%)<br>t(11;18)(q21;q21)/BIRC3-MALT1 (7%)<br>TNFαP3 inactivation (38%) |
| Lung               | 4      | *Achromobacter xylosoxidans* (40%) | t(11;18)(q21;q21)/BIRC3-MALT1 (45%)<br>t(1;14)(p22;q32)/IGH-BCL10 (8%)<br>t(14;18)(q32;q21)/IGH-MALT1 (7%)<br>TNFαP3 inactivation (9%) |
| Skin               | 4      | *Borrelia burgdorferi* (20%) | t(3;14)(p14;q32)/IGH-FOXP1 (10%)<br>t(14;18)(q32;q21)/IGH-MALT1 (7%)<br>t(11;18)(q21;q21)/BIRC3-MALT1 (4%) |
| Intestinal tract   | 2      | *Campylobacter jejuni* (50%) | t(11;18)(q21;q21)/BIRC3-MALT1 (19%)<br>t(1;14)(p22;q32)/IGH-BCL10 (7%)<br>t(14;18)(q32;q21)/IGH-MALT1 (4%)<br>TNFαP3 inactivation (9%) |
| Thyroid            | 2      | Hashimoto thyroiditis (90%) | t(3;14)(p14;q32)/IGH-FOXP1 (50%)<br>t(11;18)(q21;q21)/BIRC3-MALT1 (9%)<br>TNFαP3 inactivation (11%) |

**Table 1** Summary on the main characteristics of extranodal marginal zone lymphoma (EMZL)
Borrelia burgdorferi is a tick-borne obligate parasite and infection of humans can result in Lyme borreliosis. Moreover, Borrelia infection has been linked to cutaneous EMZL with higher detection rates in endemic areas, such as the Scottish Highlands and Austria [39, 40]. In Europe, the association varies between 10 and 42% and is almost absent in non-endemic areas [41]. However, even in non-endemic regions, like France, B. burgdorferi DNA is detected in 19% of the cases with primary cutaneous EMZL [42].

Achromobacter xylosoxidans is a rare entity representing ~ 4% of all extranodal lymphomas and 0.4% of NHL. Although pulmonary parenchyma is devoid of organized lymphoid tissue under normal physiological conditions in adults, it develops due to some disease entities, like pulmonary inflammatory process, follicular bronchiolitis, and acute infections. In one report, Achromobacter xylosoxidans, a Gram-negative bacterium with low virulence but high resistance to antibiotic therapy, has been detected with a significantly increased prevalence in patients with pulmonary EMZL as compared to non-lymphoma biopsies [43].

Viral infections

Hepatitis C virus Belonging to the Flaviviridae family of RNA viruses, hepatitis C virus (HCV) infects both hepatocytes and lymphocytes and is strongly linked to the pathogenesis of hepatocellular carcinoma and B cell NHL, including MZL. Analysis on risk factors in EMZL has clearly established an...
increased risk associated with HCV seropositivity, and HCV infection has been documented in about one-third of patients with non-gastric EMZL [44]. The causal relationship between HCV and EMZL is further substantiated by the observation of lymphoma regression after antiviral treatment [45]. EMZL in HCV-infected patients most often occurs on non-gastric sites, especially the salivary and lacrimal glands. The proposed underlying mechanisms for HCV-associated EMZL include a direct oncogenic effect of HCV-encoded proteins, an indirect antigen-driven stimulation, or immune suppression [46].

**Autoimmune disorders**

**Sjögren syndrome** Primary Sjögren syndrome (pSS) is a complex autoimmune disease that includes lacrimal and salivary gland disease, serum antibodies like anti-SSA, anti-SSB, rheumatoid factor, and salivary duct antibodies [47]. Consequently, in more than 20–40% of the patients the disease extends beyond the exocrine glands, manifested either by epithelial lymphocytic infiltration of the lungs, liver, or kidney or by immune complex-mediated phenomena such as skin vasculitis, peripheral neuropathy, and glomerular nephritis [48]. The incidence rate of pSS is 7 cases per 100,000 person-years and occurs most frequently in the fourth to seventh decades of life affecting more women than men. In patients with pSS, there is a 15-fold increased incidence of NHL that affects 5–10% of these patients, especially EMZL of the salivary glands [49, 50]. Notably, translocations involving MALT1 occur less frequently in EMZL of pSS patients [51]. However, germline mutations in BAFFR (TNFRSF13C) as well as germline and somatic coding variant of TNFAIP3 (A20) have been linked to increased risk of pSS and associated lymphoma [52, 53].

**Lymphoepithelial sialadenitis** Lymphoepithelial sialadenitis (LESA) is a benign lymphocytic infiltration of salivary gland tissue producing atrophy of the columnar ductal epithelium. In addition, there is intraepithelial infiltration of monocytoid B cells or centrocyte-like cells, which promotes proliferation of basal epithelial cells and lymphoepithelial lesions [54]. LESA is an autoimmune lesion and a component of Sjögren syndrome, but can also occur without Sjögren syndrome. The lymphoid infiltrate has a predominance of T cells, but within the foci of epithelial proliferation, lymphocytes have features of marginal zone B cells. In some cases, these foci display clonal IG rearrangements, but without evidence of progressive expansion [55]. LESA lesions are frequently controllable with corticosteroid treatment, but can progress to salivary EMZL.

**Hashimoto thyroiditis** Hashimoto thyroiditis (HT) is a common form of autoimmune thyroid disease affecting up to 2% of the general population, and more prevalent in women than men. Longstanding autoimmune HT has been directly linked to primary thyroid EMZL, which is quite a rare neoplasm accounting for 2–8% of all thyroid malignancies and 2% of all extranodal lymphomas [56]. Among patients with HT, there is a 60-fold increased risk of thyroid EMZL that affects 0.5% of the patients. The key factor in the development of HT is breakdown of immune tolerance, initiated by inflammatory events in the gland probably as a result of viral or bacterial infection or injury to the thyroid cells from toxins like iodine [57]. The injured thyroid cells may exhibit new epitopes, resulting in an influx of antigen presenting cells, clonal expansion of autoreactive T cells, and IgG producing B cells. The development of lymphoid tissue directly in the thyroid gland with progressive destruction of the thyroid cells, eventually leads to hypothyroidism [58]. The molecular pathways that contribute to lymphoma progression in HT remain to be identified, but it is interest to note that translocations involving FOXP1 occur at a relative high frequency in thyroid EMZL [59].

**Genetic alterations present in EMZL**

**Chromosomal aberrations and gene deletions**

There are several recurrent numerical and structural chromosomal aberrations linked to the pathogenesis of EMZL, including trisomy of chromosomes 3, 12, and 18, which are present in 20–30% of the EMZL cases [60–62], and the mutually exclusive chromosomal translocations t(11;18)(q21;q21)/BIRC3-MALT1, t(14;18)(q32;q21)/IGH-MALT1, t(1;14)(p22;q32)/IGH-BCL10, and t(3;14)(p14;q32)/IGH-FOXP1 [63–68] (Table 1, Fig. 2). The most common is the t(11;18)(q21;q21)/BIRC3-MALT1 translocation is previously known as API2-MALT1), which occurs in approximately 20% of the EMZL cases with a higher predominance at certain sites, such as the lung (45%) and stomach (23%), where it strongly correlates with H. pylori-independent variants of gastric EMZL [69, 70]. The BIRC3-MALT1 translocation is specific for EMZL and has not been detected in SMZL or NMZL. Translocations involving the protease and scaffold protein MALT1 or adaptor protein BCL10 result in activation of the NF-κB pathway [71], while overexpression of transcription factor FOXP1 potentiates WNT/β-catenin signaling and regulates NF-κB activity [72, 73]. Rare translocations of FOXP1 involving non-IGH partner genes have also been reported, but these may lead to aberrant expression of N-truncated isoforms of FOXP1 [68, 74, 75].

Occasionally, chromosomal translocations and gene amplifications involving transcription factor BCL6 on 3q27.3 have been described in EMZL [76]. Other rare translocations involving IGH in EMZL include t(X;14)(p11;q32)/IGH-GPR34 [77, 78], t(5;14)(q34;q32)/IGH-TEMN2, and t(9;14)(p24;q32)/IGH-KDM4C [79]. GPR34 encodes an orphan G protein-coupled receptor highly expressed in immune cells, while TEMN2 represents a teneurin transmembrane protein.
protein regulating cell-cell contact. KDM4C is one of the JmjC domain-containing histone demethylases involved in epigenetic regulation. Next to these translocations, gains of 6p25 are detected rather exclusively in 20% of the ocular adnexa EMZL cases. Furthermore, deletions on 6q23 of TNFAIP3 (A20), which acts as a negative regulator of the NF-κB pathway, are found across different anatomical sites, but preferentially in translocation-negative EMZL [80–83].

Somatic mutations

Due to aberrant somatic hypermutation caused by mistargeting of activation-induced cytidine deaminase (AID) in the germinatal center reaction, 5′ regulatory regions and coding sequences of proto-oncogenes are mutated in EMZL. Thus, mutations in the 5′ non-coding region of BCL6 have been identified in 85% of low-grade gastric lymphomas of the EMZL type [84], while somatic missense mutations in PIM1 and MYC have been reported in 30–40% of EMZL (gastric and non-gastric sites) [85, 86]. Gain-of-function mutations in EMZL have also been identified in BCL10 (6%), MYD88 (6%), which both lead to NF-κB activation, as well as in NOTCH1 (8%) and NOTCH2 (8%) in ocular adnexal EMZL [87–90]. In this same tumor type, inactivating mutations have been found in TNFAIP3 (27–54%), TBL1XR1 (18%), CREBBP (17%), TP53 (8%), and KMTD2 (6–22%) [89, 91].

Activation of the NF-κB pathway in EMZL

NF-κB consists of a family of dimeric transcription factors that are critical for both innate and adaptive immune responses [92]. There are five NF-κB subunits, including RelA (p65), RelB, c-Rel, NF-κB1 (p50 and its precursor p105), and NF-κB2 (p52 and its precursor p100), which are kept inactive in the cytoplasm by their inhibitors (IκBα, IκBβ, and IκBε) or in its dormant precursor form. RelB forms transcriptional inactive complexes with the subunits RelA and c-Rel. NF-κB activation is mediated by two parallel signaling pathways, termed the canonical (classical) and non-canonical (alternative) NF-κB pathway that under normal physiological conditions involves a highly regulated process of transient activation in response to extracellular signals (Fig. 3). The canonical pathway is activated by stimulation of specific receptors, such as the BCR, TLR, and interleukin 1 receptor (IL1R). Each of these receptors engages distinct adaptor molecules, but all converge on the canonical NF-κB pathway, which involves IκB phosphorylation by the IκB kinase (IKK) complex, inducing its K48-linked polyubiquitination and subsequent degradation by the proteasome. As a result, NF-κB homo- and heterodimers are released permitting their translocation to the nucleus and transcriptional regulation of NF-κB target genes. The non-canonical NF-κB pathway consists of successive activation of NF-κB inducible kinase (NIK) and IKKα, leading to phosphorylation and partial proteolysis of NF-κB2 (p100), thereby generating the functional active form p52 that associates with RelB, and upon nuclear translocation regulates transcription [92].

Stimulation of TLR and IL1R triggers dimerization and conformational change of the Toll/IL1R homologous (TIR) domain, which results in recruitment of MYD88, interleukin-1 receptor-associated kinase-4 (IRAK4) and IRAK1, forming the Myddosome complex that is capable of activating the IKK complex and activation of the canonical NF-κB pathway [93].
In-frame deletions and hotspot mutations of MYD88, such as p.L265P in the TIR domain, are found in about 19% of the ocular adnexal EMZL cases [89], which yields a gain-of-function phenotype resulting in spontaneous assembly of the Myddosome and activation of NF-κB.

Engagement of the BCR triggers tyrosine phosphorylation of immunoreceptor tyrosine-based activation motif (ITAM) of CD79A and CD79B, which results in recruitment of spleen tyrosine kinase (SYK). Through subsequent activation of Bruton’s tyrosine kinase (BTK) and protein kinase C (PKC) signaling, the scaffold protein CARD11 (CARMA1) is recruited, which upon a conformational change is able to interact with adaptor protein BCL10, thereby promoting its polymerization and filament formation leading to assembly of the CARD11/BCL10/MALT1 (CBM) signalosome complex [94]. The CBM complex recruits then TNFR-associated factor-6 (TRAF6), transforming growth factor β activating kinase-1 (TAK1) and TAK binding protein-2/3 (TAB2/3), which leads to activation of the IKK complex and stimulation of the canonical NF-κB signaling pathway [95]. Overexpression of BCL10 due to t(1;14)(p22;q32) causes its constitutive activation through oligomerization via its N-terminal caspase recruitment domain (CARD)/CARD interaction, thus leading to enhanced NF-κB signaling. BCL10 also regulates the non-canonical NF-κB pathway, which normally acts downstream of receptors, like CD40 and B cell activating factor receptor (BAFFR).

The paracaspase MALT1 is an Arg-specific protease that contains several functional domains including an N-terminal...
death domain, three immunoglobulin (Ig)-like domains and a proteolytically active caspase-like domain [96]. As a result of t(14;18)(q32;q21), increased levels of MALT1 facilitate the interaction with BCL10 through its N-terminal Ig-like domains, which triggers its own oligomerization and activation, thus enhancing canonical NF-κB signaling (Fig. 4a). Furthermore, through its protease activity, MALT1 also promotes the specific cleavage of several negative regulators of NF-κB, which includes TNFAIP3, BCL10, CYLD, and RelB [97] (Fig. 4a). TNFAIP3 can inactivate a number of NF-κB signaling molecules, like receptor-interacting protein 1/2 (RIP1/2), TRAFF6, and IKKγ (NEMO). Thus, TNFAIP3 deletions and inactivating mutations, which are predominantly observed in translocation-negative EMZL of ocular adnexa (30%), salivary glands (8%), and thyroid (11%), augment NF-κB signaling downstream of multiple surface receptors [82, 98].

Recently, another substrate of MALT1 has been identified that is also linked to regulation of the NF-κB pathway [99, 100]. This involves HOIL1(RBCK1), a component of the linear ubiquitin chain assembly complex (LUBAC), which comprises of HOIL1, HOIP(RNF31), and Sharpin. LUBAC promotes NF-κB activation by addition of linear (N-terminal linked) polyubiquitin chains on its substrates. MALT1-dependent RBCK1 cleavage reduces linear

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**Fig. 4** Regulation of the NF-κB signaling pathway by MALT1 and BIRC3-MALT1. **a** Overview of MALT1-dependent activation and regulation of the NF-κB pathway via its adaptor and protease functions. Through its adaptor functions, it recruits the CARD11/BCL10/TRAF6 complex, which results in polyubiquitination and degradation of NEMO, thereby activating the IKK complex, which phosphorylates IkB and activates NF-κB. MALT1 protease activity controls NF-κB activation by promoting the degradation of both positive (HOIL1, RelB, BCL10) and negative (TNFAIP3, CYLD) regulators of this pathway. **b** The chimeric fusion protein BIRC3-MALT1 is created by the chromosomal translocation t(11;18)(q21;q21) in extranodal marginal zone lymphoma. The oncogenic potential of BIRC3-MALT1 relies on its ability to activate both the canonical and non-canonical pathways through multiple mechanisms. BIRC3-MALT1 is activated through auto-oligomerization, which results in the recruitment of TRAF2/RIP1 via the BIRC3 moiety that triggers RIP1 ubiquitination and canonical NF-κB activation. In addition, recruitment of TRAF6/TAB/TAK1 induces NEMO ubiquitination and also canonical NF-κB signaling. In parallel, BIRC3-MALT1 causes deregulated MALT1 paracaspase activity, which results in proteolytic cleavage of NIK, creating a constitutively active NIK fragment that stimulates IKKα and the non-canonical NF-κB pathway.
ubiquitination of cellular proteins and has thus been proposed to provide negative feedback on the NF-κB pathway.

The BIRC3-MALT1 fusion protein resulting from t(11;18)(q21;q21) gains novel functions through its ability to constitutively activate both canonical and non-canonical NF-κB pathways [101] (Fig. 4b). BIRC3 belongs to the inhibitor of apoptosis (IAP) family of proteins and contains three tandem copies of the baculovirus IAP repeat (BIR) domain, a CARD and a C-terminal RING domain. Several variants of the BIRC3-MALT1 fusion are present in patients with t(11;18)(q21;q21) translocation [65, 102, 103]. In all cases, the breakpoints within BIRC3 occur consistently between the third BIR and the CARD domain, whereas the breakpoints within MALT1 retain the C-terminal caspase-like domain. The BIRC3-MALT1 fusion is capable of auto-oligomerization, recruitment of TRAF2/RIP1 and TRAF6/TAB/TAK1 complexes, as well as cleavage of TNFAIP3 and CYLD, thereby activating the canonical NF-κB pathway. In addition, the BIRC3 moiety of the fusion protein recruits NIK, leading to its cleavage by the MALT protease domain [104]. The resulting truncated NIK kinase domain is resistant to TRAF3-dependent proteosomal degradation, leading to constitutive activation of the non-canonical NF-κB pathway. Finally, the BIRC3-MALT1 fusion protein has also the ability to cleave the tumor suppressor protein LIM domain and actin-binding protein-1 (LIMA1), thereby generating a novel onco-genic LIM domain only (LMO) fragment [105].

**Progression and histological transformation of EMZL**

EMZL is normally presented as a low-grade tumor, but in some cases gradually develops into a more aggressive large B cell lymphoma with often complete transformation into DLBCL. During this transition, composite lymphomas may exist showing fields of clonally related small and large cell areas. Histological transformation to DLBCL has been observed between 3 and 4% [106, 107] and 8–11% of the EMZL cases [5, 108]. Although there is a stronger tendency of t(1;18)-negative EMZL to transform into DLBCL [109, 110], the presence of BIRC3-MALT translocation in gastric EMZL does not exclude progression to DLBCL [111, 112]. Progression of low-grade lymphoma toward high-grade lymphoma is facilitated by complete loss of p16INK4a and TP53 gene function [113, 114]. Furthermore, chromosomal translocations involving BCL6 [115–117], or CCND3 [118], as well as MYC overexpression [119], and strong nuclear FOXP1 expression [120] are found in DLBCL transformation. In addition, upregulation of the chemokine receptors CXCR3 and CXCR7 has been correlated with progression of gastric EMZL into DLBCL [121].

**Diagnosis of EMZL**

The diagnosis of EMZL can be rather challenging, as extranodal sites of disease are sometimes difficult to access, resulting in small biopsy samples. The optimal diagnosis of EMZL requires integration of clinical, histopathological, and molecular information.

**Histopathological findings**

In many cases, EMZL consists of multifocal, small, or confluent, clonally identical foci of malignant cells that colonize the germinal center and are scattered throughout the involved organ. EMZL shows a morphological spectrum, ranging from mixtures of heterogeneous B cells, including monocytoïd and plasmacytoïd B cells, small lymphocytes, and centrocytes to monomorphic proliferations of monocytoïd B cells. In about one-third of the cases, prominent plasmacytic differentiation is observed. Besides the tumor cells, additional reactive cells are present, consisting mainly of T lymphocytes. Other histological features include remnants of reactive follicular hyperplasia and infiltration of glands or crypts of adjacent tissue accompanied by architectural destruction, resulting in lymphoepithelial lesions (LEL). The EMZL cells are positive for CD20, CD22, CD35, CD79a, BCL2, and IgM, while usually negative for CD5, CD10, CD23, cyclin D1, BCL6, and IgD, and many of these markers are informative for differential diagnosis. Both flow cytometry and immunohistochemistry can be performed to detect the expression of these markers. Additional immunohistochemical markers that are informative include MNDA and IRTA1 [122–125], as well as the detection of MALT1 and BCL10 nuclear/cytoplasmic protein levels in 18q21 and 1p22 translocation-positive EMZL [64, 126, 127].

**Molecular diagnostics**

**IG clonality testing** Although histopathological examination remains the gold standard for diagnosis, the detection of monoclonality of immunoglobulin (IG) gene rearrangements, preferably using the EuroClonality/BIOMED-2 primer sets and protocols, represents a useful aid [128]. Especially, inclusion of incomplete IGH-DJ joining as a clonality target is very informative, since clonal IGH-DJ rearrangements occur in many EMZL cases. Furthermore, clonal IGH-DJ rearrangements are exclusively present in 5–8% of clonal B cell populations in the absence of detectable IGH-VJ rearrangements [129]. Although not part of the routine diagnostic workup, sequence analysis of the rearranged IGHV genes in EMZL have further provided evidence for antigen mediated affinity maturation by the restricted use of certain sequences. In extranodal lymphomas located at the ocular adnexa and salivary glands there is biased usage of IGHV4-34 and IGHV1-69,
respectively, while those in the stomach appear to have over-representation of IGHV3-7 and IGHV1-69 usage [130–132].

**Detection of chromosomal aberrations by FISH and RT-PCR** The detection of common cytogenetic abnormalities by interphase fluorescence in situ hybridization (FISH) has been proven to be informative for the diagnosis of EMZL [133, 134]. FISH is used for the detection of chromosomal translocations involving IGH, MALT1, FOXP1, and BCL10, as well as numerical chromosomal abnormalities, including deletions and trisomy of chromosome 3, 12, and 18 [59, 133, 135, 136]. However, it should be emphasized that while positive FISH together with clinical and morphological features of EMZL is very helpful in the diagnosis, negative FISH should not exclude the diagnosis of EMZL. Through the identification of the specific genomic regions rearranged in EMZL, routine reverse transcription polymerase chain reaction (RT-PCR) has also been implemented for the detection of genomic translocations and the presence of fusion transcripts, such as BIRC3-MALT1[137, 138]. Moreover, detection of BIRC3-MALT1 in gastric EMZL has therapeutic implications (see below).

**Therapeutic strategies for EMZL**

The involvement of infectious agents in the pathogenesis of EMZL has provided opportunities toward unique therapeutic approaches for lymphoma treatment. Many patients with ocular adnexa EMZL respond to doxycycline treatment and show lymphoma regression in 65% of the patients [139]. Likewise, for stages I and II of gastric EMZL, the initial treatment of choice is *H. pylori* eradication, which results in complete remission in about 80% of patients with gastric EMZL [140–142]. The most commonly used regimen includes a proton pump inhibitor (omeprazole) in combination with amoxicillin and clarithromycin. Notably, EMZL harboring t(11;18) and t(1;14) translocations are associated with resistance to *H. pylori* eradication therapy [70, 141]. *H. pylori*-negative patients also respond to antibiotic treatment, since other microorganisms are known to be involved in the pathogenesis of gastric EMZL, and complete remission can be achieved in 57% of these patients [143]. Patients with symptomatic systemic disease, mainly those with disseminated stages III and IV, are considered for treatment with chemotherapy (e.g., bendamustine, fludarabine, or chlorambucil) combined with P3K inhibitors and mTOR inhibitor everolimus. Activation of NF-κB itself, which may also result by loss of TNFAIP3 function due to gene deletions or mutations [*], can be blocked by bortezomib. Lenalidomide promotes degradation of IKZF1 and IKZF3, thereby downregulating the expression of MYC and IRF4. Transcription factors FOXP1 and BCL6, which are upregulated by genetic alterations (e.g., chromosomal translocations, promoter mutations), as well as other epigenetic regulators that require HDAC activity, can be blocked by the action of HDAC inhibitors.
either anti-CD20 antibody rituximab or the immunomodulatory drug lenalidomide [144–146]. First-line treatment combining chlorambucil with rituximab has shown improved survival as compared to chlorambucil or rituximab alone [146]. Combination therapy of rituximab with lenalidomide has also been demonstrated to be effective [147], along with cyclophosphamide and dexamethasone [148]. The more aggressive types of chemotherapy regimens, including CHOP (cyclophosphamide, doxorubicine, vincristine, and prednisone), are often reserved for patients with transformation to high-grade lymphomas.

Alternative therapies for EMZL involving new agents include inhibitors of mTOR (everolimus) [149], HDAC (vorinostat) [150, 151], proteasome (bortezomib) [152], BTK (ibrutinib) [153, 154], and PI3Kδ (idelalisib) [155] (Fig. 5). Many of these drugs are under investigation in clinical trials, of which some show positive response rates, but improvement on long-term overall survival remains to be demonstrated. Targeted therapy directed against the MALT1 paracaspase protein has also been exploited for therapeutic intervention. Several inhibitors have been identified that show promising results in activated B cell-DLBCL [156–158], but their effectiveness in EMZL remains to be established.

Conclusions

During the past two decades, new insight has been gained into the pathobiology of EMZL, which revealed a complex interplay between chronic inflammation and genetic abnormalities that seem to converge on deregulation of specific signaling cascades that often result in activation of the NF-κB pathway. This knowledge has lead to new developments in clinical diagnostics and has opened interesting opportunities for more targeted therapeutic intervention. Further understanding of which specific molecules within these signaling pathways are essential in promoting and maintaining lymphomagenesis may lead to novel therapy modalities, which will be especially relevant for managing the more aggressive forms of EMZL.

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References

1. Thieblemont C (2005) Clinical presentation and management of marginal zone lymphomas. Hematol Am Soc Hematol Educ Program 307–313. https://doi.org/10.1182/asheducations.2005.1.307
2. Du MQ (2016) MALT lymphoma: a paradigm of NF-kappaB dysregulation. Semin Cancer Biol 39:49–60. https://doi.org/10.1016/j.semcancer.2016.07.003
3. Zucca E, Berti F, Vannata B, Cavalli F (2014) Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. Clin Cancer Res: Off J Am Assoc Cancer Res 20(20): 5207–5216. https://doi.org/10.1158/1078-0432.CCR-14-0496
4. Olszewski AJ, Castillo JJ (2013) Survival of patients with marginal zone lymphoma: analysis of the surveillance, epidemiology, and end results database. Cancer 119(3):629–638. https://doi.org/10.1002/cncr.27777
5. Meyer AH, Stroux A, Lerch K, Eucker J, Eitle J, Hohloch K, Andrzejak M, Possinger K, Dorken B, Pezzuto A, Scholz CW (2014) Transformation and additional malignancies are leading risk factors for an adverse course of disease in marginal zone lymphoma. Ann Oncol: Off J Eur Soc Med Oncol/ESMO 25(1):210–215. https://doi.org/10.1093/annonc/mdt507
6. Sretenovic M, Colovic M, Jankovic G, Suvajdzic N, Mihaljevic B, Colovic N, Todorovic M, Atkinson HD (2009) More than a third of non-gastric mALT lymphomas are disseminated at diagnosis: a single center survey. Eur J Haematol 82(5):373–380. https://doi.org/10.1111/j.1600-0609.2009.01217.x
7. Thieblemont C, Berger F, Dumontet C, Mouillet I, Bouafia F, Feldman P, Salles G, Goffinet B (2000) Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 95(3):802–806
8. Berti F, Cazzaniga G, Bossard G, Roggero E, Barbazza R, De Boni M, Capella C, Pedrinis E, Cavalli F, Biondi A, Zucca E (1997) Immunoglobulin heavy chain diversity genes rearrangement pattern indicates that MALT-type gastric lymphoma B cells have undergone an antigen selection process. Br J Haematol 97(4):830–836
9. Craig VI, Arnold I, Gerke C, Huynh MQ, Wundisch T, Neubauer A, Renner C, Falkow S, Muller A (2010) Gastric MALT lymphoma B cells express polyreactive, somatically mutated immunoglobulins. Blood 115(3):581–591. https://doi.org/10.1182/blood-2009-06-228015
10. Wohrer S, Troch M, Streubel B, Zwerina J, Skrabs C, Formanek MJ, Hauff W, Hoffmann M, Mullauer L, Chott A, Raderer M (2007) MALT lymphoma in patients with autoimmune diseases: a single center survey. Eur J Haematol 82(5):373–380. https://doi.org/10.1111/j.1600-0609.2009.01217.x
11. Ekstrom Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, Spinelli JJ, La Vecchia C, Zheng T, Becker N, De Sanjose S, Chiu BC, Dal Maso L, Cocco P, Maynadie M, Foretova L, Staines A, Brennan P, Davis S, Severson R, Cerhan JR, Breen EC, Birmann B, Grulich AE,
12. Luminari S, Cesaretti M, Marcheselli L, Rashid I, Madrigali S, Maiorana A, Federico M (2010) Decreasing incidence of gastric MALT lymphomas in the era of anti-Helicobacter pylori interventions: results from a population-based study on exonational marginal zone lymphomas. Ann Oncol Off J Eur Soc Med Oncol/ESMO 21(4):855–859. https://doi.org/10.1093/annonc/mdp402
13. Hussel T, Isaacsen PG, Crabtree JE, Spencer J (1993) The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. Lancet 342(8871):571–574
14. Munari F, Lonardi S, Cassatella MA, Doglioni C, Cangi MG, Amedei A, Facchetti F, Eishi Y, Rugge M, Fassan M, de Bernard M, D’Elios MM, Vermi W (2011) Tumor-associated macrophages as major source of APRIL in gastric MALT lymphoma. Blood 117(24):6612–6616. https://doi.org/10.1182/blood-2010-06-293266
15. Wang HP, Zhu YL, Shao W (2013) Role of Helicobacter pylori virulence factor cytotoxin-associated gene A in gastric mucosa-associated lymphoid tissue lymphoma. World J Gastroenterol 19(45):8219–8226. https://doi.org/10.3748/wjg.v19.i45.8219
16. Tohidpour A (2016) CagA-mediated pathogenesis of Helicobacter pylori. Microb Pathog 93:44–55. https://doi.org/10.1016/j.micpath.2016.01.005
17. Lin WC, Tsai HF, Kuo SH, Wu MS, Lin CW, Hsu PI, Cheng AL, Maorana A, Federico M (2010) Decreasing incidence of gastric MALT lymphomas in the era of anti-Helicobacter pylori interventions: results from a population-based study on exonational marginal zone lymphomas. Ann Oncol Off J Eur Soc Med Oncol/ESMO 21(4):855–859. https://doi.org/10.1093/annonc/mdp402
18. Selbach M, Moese S, Hauck CR, Meyer TF, Backert S (2002) Src virulence factor cytotoxin-associated gene A in gastric mucosa- associated lymphoid tissue to Helicobacter pylori. Microb Pathog 34:46–53. https://doi.org/10.1006/micp.2002.0730
19. Poppe M, Feller SM, Romer G, Wessler S (2007) Phosphorylation of Helicobacter pylori CagA by c-Abl leads to cell motility. Oncogene 26(24):3462–3472. https://doi.org/10.1038/sj.onc.1210139
20. Higashi H, Tsutsuini R, Muto S, Sugiyama T, Azuma T, Asaka M, Hatakeyama M (2002) SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein. Science 295(5555):683–686. https://doi.org/10.1126/science.1067147
21. Zhu Y, Wang C, Huang J, Ge Z, Dong Q, Zhong X, Su Y, Zheng S (2007) The Helicobacter pylori virulence factor CagA promotes Erk1/2-mediated basal phosphorylation in lymphocytes: a mechanism of CagA-inhibited lymphocyte apoptosis. Cell Microbiol 9(4):952–961. https://doi.org/10.1111/j.1462-5822.2006.00843.x
22. Kuo SH, Chen LT, Lin CW, Yeh KH, Shun CT, Tseng YS, Liou JM, Wu MS, Hsu PN, Cheng AL. (2016) Expressions of the CagA protein and CagA-signaling molecules predict H. pylori-infection of early-stage gastric DLBCL. Blood. https://doi.org/10.1182/blood-2016-04-67179
23. Buti L, Spooner E, Van der Veen AG, Rappuoli R, Covacci A, Piolegg HL (2011) Helicobacter pylori cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. Proc Natl Acad Sci U S A 108(22):9238–9243. https://doi.org/10.1073/pnas.1106021108
24. Umehara S, Higashi H, Ohnishi N, Asaka M, Hatakeyama M (2003) Effects of Helicobacter pylori CagA protein on the growth and survival of B lymphocytes, the origin of MALT lymphoma. Oncogene 22(51):8337–8342. https://doi.org/10.1038/sj.onc.1207028
25. Ohmae T, Hirata Y, Maeda S, Shibata W, Yanai A, Ogura K, Yoshida H, Kawabe T, Omata M (2005) Helicobacter pylori actives NF-kappaB via the alternative pathway in B lymphocytes. J Immunol 175(11):7162–7169
26. Haesebruck F, Pasmans F, Flahou B, Smet A, Vandamme P, Ducattelle R (2011) Non-Helicobacter pylori Helicobacter species in the human gastric mucosa: a proposal to introduce the terms H. heilmannii sensu lato and sensu stricto. Helicobacter 16(4):339–340. https://doi.org/10.1111/j.1523-5378.2011.00849.x
27. Bento-Miranda M, Figueiredo C (2014) Helicobacter heilmannii sensu lato: an overview of the infection in humans. World J Gastroenterol 20(47):17779–17787. https://doi.org/10.3748/wjg.v20.i47.17779
28. Stolte M, Bayerdorffer E, Morgen A, Alpen B, Wundsich T, Thiede C, Neubauer A (2002) Helicobacter pylori and gastric MALT lymphoma. Gut 50(Suppl 3):III19–III24
29. Ferreri AJ, Guidoboni M, Ponzone M, De Concilis C, Dell’Oro S, Fleischhauer K, Caggiali L, Lettini AA, Dal Cin E, Ieri R, Freschi M, Villa E, Boiocchi M, Dolceti R (2004) Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. J Natl Cancer Inst 96(8):586–594
30. Ferreri AJ, Ponzone M, Guidoboni M, Resti AG, Politi LS, Cortelazzo S, Demeter J, Zallio F, Palmas A, Mutti G, Dogini GP, Pasini E, Lettini AA, Sacchetti F, De Concilis C, Doglioni C, Dolceti R (2006) Bacteria-eradicating therapy with doxycycline in ocular adnexal MALT lymphoma: a multicenter prospective trial. J Natl Cancer Inst 98(19):1375–1382. https://doi.org/10.1093/jnci/dji237
31. Chanudet E, Zhou Y, Bacon CM, Wotherspoon AC, Muller-Hermelink HK, Adam P, Dong HY, de Jong D, Li Y, Wei R, Gong X, Wu Q, Ranaldi R, Goteri G, Pileri SA, Ye H, Hamoudi RA, Liu H, Radford J, Du MQ (2006) Chlamydia psittaci is variably associated with ocular adnexal MALT lymphoma in different geographical regions. J Pathol 209(3):344–351. https://doi.org/10.1002/path.1984
32. Daibata M, Nemoto Y, Togitani K, Fukushima A, Ueno H, Ouchi K, Fukushima H, Imai S, Taguchi H (2006) Absence of Chlamydia psittaci in ocular adnexal lymphoma. Br J Haematol 132(5):651–652. https://doi.org/10.1111/j.1365-2141.2005.05943.x
33. Rosado MF, Byrne GE Jr, Ding F, Fields KA, Ruiz P, Dubovy SR, Walker GR, Markoe A, Lossos IS (2006) Ocular adnexal lymphoma: a clinicopathologic study of a large cohort of patients with no evidence for an association with Chlamydia psittaci. Blood 107(2):467–472. https://doi.org/10.1182/blood-2005-06-2332
34. Husain A, Roberts D, Pro B, McLaughlin P, Esmaeili B (2007) Meta-analyses of the association between Chlamydia psittaci and ocular adnexal lymphoma and the response of ocular adnexal lymphoma to antibiotics. Cancer 110(4):809–815. https://doi.org/10.1002/cncr.22843
35. Ponzone M, Ferreri AJ, Guidoboni M, Lettini AA, Cangi MG, Pasini E, Sacchi L, Pecciarini L, Grassi S, Dal Cin E, Stefano R, Magnino S, Dolceti R, Doglioni C (2008) Chlamydia infection and lymphomas: association beyond ocular adnexal lymphomas highlighted by multiple detection methods. Clin Cancer Res: Off J Am Assoc Cancer Res 14(18):5794–5800. https://doi.org/10.1158/1078-0432.CCR-08-0676
36. Dingle KE, Van Den Braak N, Colles FM, Price LJ, Woodward DL, Rodgers FG, Endtz HP, Van Belkum A, Maiden MC (2001) Sequence typing confirms that Campylobacter jejuni strains associated with Guillain-Barre and Miller-Fisher syndromes are of diverse genetic lineage, serotype, and flagella type. J Clin Microbiol 39(9):3346–3349
37. Lecuit M, Abachin E, Martin A, Poyart C, Pochart P, Suarez F, Bengoufa D, Feuillard J, Lavergne A, Gordon JI, Berche P, Guillemin L, Lorholary O (2004) Immunoproliferative small
intestinal disease associated with Campylobacter jejuni. N Engl J Med 350(3):239–248. https://doi.org/10.1056/NEJMoa031887

38. Ben-Ayed F, Halphen M, Najar T, Boussene H, Jaafoura H, Bouguerra A, Ben Salah N, Mourali N, Ayed K, Ben Khalifa H et al (1989) Treatment of alpha chain disease. Results of a prospective study in 21 Tunisian patients by the Tunisian-French Intestinal Lymphoma Study Group. Cancer 63(7):1251–1256

39. Goodlad JR, Davidson MM, Hollowood K, Ling C, MacKenzie C, Christie I, Batstone PJ, Ho-Yen DO (2000) Primary cutaneous B-cell lymphoma and Borrelia burgdorferi infection in patients from the highlands of Scotland. Am J Surg Pathol 24(9):1279–1285

40. Cerroni L, Zochling N, Putz B, Kerl H (1997) Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. J Cutan Pathol 24(8):457–461

41. Ponzoni M, Ferreri AJ, Mappa S, Pasini E, Govi S, Facchetti F, Morcillo C, Jimenez-Heredia I, Sanchez-Berna I, Lopez-Fanlo P, Guisado-Vasco P, Perez-Alvarez R, Chamorro AJ, Estrada S, Martinez JM, Lucioni M, Pizzolo G (2004) Most cases of primary salivary gland lymphoma are associated in patients by the Tunisian-French Intestinal Lymphoma Study Group. Cancer 63(7):1251–1256

42. de la Fouchardiere A, Vandenesch F, Berger F (2003) Borrelia burgdorferi and cutaneous B-cell lymphoma. J Cutan Pathol 24(8):457–461

43. Adam P, Czapsiewski P, Colak S, Kosmidis P, Toussey M, Sagnaert X, Boudova L, Okon K, Morresi-Hauf A, Agostinelli C, Plani S, Pruneri G, Martinelli G, Du MQ, Fend F (2014) Prevalence of Achromobacter xylosoxidans in pulmonary mucosa-associated lymphoid tissue lymphoma in different regions of Europe. Br J Haematol 164(6):804–810. https://doi.org/10.1111/bjh.12703

44. Luppi M, Longo G, Ferrari MG, Ferrara L, Marasca R, Barozzi P, Morcelli M, Emilia G, Torelli G (1996) Additional neoplasms and HCV infection in low-grade lymphoma of MALT type. Br J Haematol 90(3):197–203. https://doi.org/10.1046/j.1365-2141.1996.12004.x

45. Michot JM, Canioni D, Driss H, Alric L, Cacoub P, Suarez F, Sibon D, Thieblemont C, Dupuis J, Terrier B, Fayet C, Tilly H, Pol S, Leblond V, Settegrana C, Ravidra P, Barthe Y, Hendel-Chavez H, Nguyen-Khac F, Merle-Beral H, Berger F, Molina T, Charlotte F, Carrat F, Davi F, Hermine O, Besson C, Group AH-LS (2015) Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas. ANRS HC-13 lympho-C study. Am J Hematol 90(3):197–203. https://doi.org/10.1002/ajh.23889

46. Marcucci F, Mele A (2011) Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. Blood 117(6):1792–1798. https://doi.org/10.1182/blood-2010-06-275818

47. Skopoulji FN, Dafni U, Ioannidis JP, Moutsopoulos HM (2000) Clinical evolution, and morbidity and mortality of primary Sjogren’s syndrome. Semin Arthritis Rheum 29(5):296–304. https://doi.org/10.1016/s0049-0172(00)00493-x

48. Papageorgiou A, Voulgaris M, Tzioufas AG, Moutsopoulos HM, Vouglarelis M, Morcillo C, Jimenez-Heredia I, Sanchez-Berna I, Lopez-Guillermo A, Ramos-Casals M, GEAS-SEMI SSSG (2017) Characterization and risk estimate of cancer in patients with primary Sjogren syndrome. J Hematol Oncol 10(1):90. https://doi.org/10.1186/s13045-017-0464-5

49. Ambrosetti A, Zanotti R, Pattaro C, Lenzi L, Chilosi M, Caramaschi P, Arcaini L, Pasini F, Biasi D, Orlandi E, D’Adda M, Lucioni M, Pizzolo G (2004) Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjogren syndrome or hepatitis C virus infection. Br J Haematol 126(1):43–49. https://doi.org/10.1111/j.1365-2141.2004.04993.x

50. Brito-Zeron P, Kostov B, Fraile G, Caravia-Duran D, Maure B, Rascon FJ, Zamora M, Casanos A, Lopez-Dupla M, Ripoll M, Pinilla B, Fonseca E, Akasbi M, de la Red G, Duarte-Millan MA, Fanlo P, Guisado-Vasco P, Perez-Alvarez R, Chamorro AJ, Morcillo C, Jimenez-Heredia I, Sanchez-Berna I, Lopez-Guillermo A, Ramos-Casals M, GEAS-SEMI SSSG (2017)
large B-cell lymphoma of primary gastric origin. Cancer Genet Cyto-genet 97(2):114–118.

117. Flossbach L, Antonea E, Buck M, Siebert R, Mattfeld T, Moller P, Barth TF (2011) BCL6 gene rearrangement and protein expression are associated with large cell presentation of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Int J Cancer 129(1):70–77. https://doi.org/10.1002/ijc.25663

118. Sonoki T, Harder L, Horsman DE, Karran L, Taniguchi I, Willis TG, Gesk S, Steinenmann D, Zucca E, Schlegelberger B, Sole F, Mungall AJ, Gascoyne RD, Siebert R, Dyer MJ (2001) Cyclin D3 is a target gene of t(6;14)(p21.1;q32.3) of mature B-cell malignancies. Blood 98(9):2837–2844

119. Huang W, Guo L, Liu H, Zheng B, Ying J, Lv N (2014) C-MYC overexpression predicts aggressive transformation and a poor outcome in mucosa-associated lymphoid tissue lymphomas. Int J Clin Exp Pathol 7(9):5634–5644

120. Sagaert X, de Paepe P, Libbrecht L, Vanhentenrijk V, Verhoef G, Thomas J, Wlodarska I, De Wolf-Peeters C (2006) Forkhead box protein P1 expression in mucosa-associated lymphoid tissue lymphomas predicts poor prognosis and transformation to diffuse large B-cell lymphoma. J Clin Oncol Off J Am Soc Clin Oncol 24(16):2490–2497. https://doi.org/10.1200/JCO.2006.05.6150

121. Deutsch AJ, Steinbauer E, Hofmann NA, Strunk D, Gerlza T, Sagaert X, Laurent M, Baens M, Wlodarska I, De Wolf-Peeters C (2006) MALT1 and BCL10 aberrations in MALT lymphomas and is useful in the differential diagnosis with nodal marginal zone lymphoma. Leukemia 23(10):1847–1857. https://doi.org/10.1038/leu.2006.108

122. Metcalf RA, Monabati A, Vyas M, Roncador G, Gualco G, Bacchi ST, van Noesel CJ, Bende RJ (2012) Chlamydia psittaci-negative ocular adenomal marginal zone B-cell lymphomas have biased VH4-34 immunoglobulin gene expression and proliferate in a distinct inflammatory environment. Leukemia 26(7):1647–1653. https://doi.org/10.1038/leu.2012.28

123. Falini B, Agostinelli C, Bigerna B, Pucciarini A, Pacini R, Gaulard P, Jasani B, Garcia JF, Ott M, Hannsmann ML, Berger F, Hummel M, Davi F, Bruggemann M, Lavender FL, Schuuring E, Evans PA, White H, Salles G, Groenen PJ, Gameiro P, Dongen JJ (2007) Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia 21(2):201–206. https://doi.org/10.1038/sj.leu.2404467

124. Evans PA, Pott C, Groenen PJ, Salles G, Davi F, Berger F, Garcia JF, van Krieken JH, Pals S, Kluin P, Schuuring E, Sparrargen M, Boone E, Gonzalez D, Martinez B, Villuendas R, Gameiro P, Diss TC, Mills K, Morgan GJ, Carter GI, Milner BJ, Pearson D, Hummel M, Jung W, Ott M, Canioni D, Beldjord K, Bastard C, Della-Furau MH, van Dongen J, Molina TJ, Cabecadas J (2007) Significantly improved PCR-based clonality testing in B-cell malignancies by use of multiple immunoglobulin gene targets. Report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia 21(2):207–214. https://doi.org/10.1038/sj.leu.2404479

125. van Maldegem F, Wormhoudt TA, Mulder MM, Oud ME, Schilder-Tol E, Musler AR, Aten J, Saeed P, Kresten MJ, Pals ST, van Noesel CJ, Bende RJ (2012) Myeloid cell receptor receptors in gastric MALT lymphoma: loss of CXCR4 and upregulation of CXCR7 is associated with progression to diffuse large B-cell lymphoma. Mod Pathol 25(2):182–194. https://doi.org/10.1038/modpathol.2012.134

126. Ye H, Gong L, Liu H, Hamoudi RA, Shirali S, Ho L, Chott A, Thomas J, Wlodarska I, De Wolf-Peeters C (2014) Myeloid cell protein P1 expression in mucosa-associated lymphoid tissue lymphoma-associated chromosomal abnormalities in routine diagnostic analysis of the novel marginal zone B-cell marker IRTA1 in marginal zone lymphomas and is useful in the differential diagnosis with follicular lymphoma. Hum Pathol 45(8):1730–1736. https://doi.org/10.1016/j.humpath.2014.04.004

127. Falini B, Agostinelli C, Bigerna B, Pucciarini A, Pacini R, Tabarrini A, Falcinelli F, Picciolo M, Pauli M, Gambacorta M, Ponzoni M, Paiace E, Ascani S, Martelli MP, Dalla Favera R, Stein H, Pileri SA (2012) IRTA1 is selectively expressed in nodal and extranodal marginal zone lymphomas. Histopathology 61(5):930–941. https://doi.org/10.1111/j.1365-2559.2012.04289.x

128. Ikeda JI, Kohara M, Tsuruta Y, Nojima S, Tahara S, Ohshima K, Kurashige M, Wada N, Morii E (2017) Immunohistochemical analysis of the novel marginal zone B-cell marker IRTA1 in malignant lymphoma. Hum Pathol 59:70–79. https://doi.org/10.1016/j.humpath.2016.09.011

129. Ye H, Gong L, Liu H, Hamoudi RA, Shirali S, Ho L, Chott A, Streubel B, Siebert R, Gesk S, Martin-Sabero JI, Radford JA, Banerjee S, Nicholson AG, Ranaldi R, Remstein ED, Gao Z, Zheng J, Isaacson PG, Dogan A, Du MQ (2005) MALT lymphoma with t(11;18)(q21;q21)/IGH-MALT1 is characterized by strong cytoplasmic MALT1 and BCL10 expression. J Pathol 205(3):293–301. https://doi.org/10.1002/path.1715

130. Sagaert X, Laurent M, Baens M, Wlodarska I, De Wolf-Peeters C (2006) MALT1 and BCL10 aberrations in MALT lymphomas and their effect on the expression of BCL10 in the tumour cells. Mod Pathol 19(2):225–232. https://doi.org/10.1038/modpathol.2006.11

131. van Krieken JH, Langerak AW, Macintyre EA, Kneba M, Hodges E, Sanz RG, Morgan GJ, Parreira A, Molina TJ, Cabecadas J, Gaulard P, Jasani B, Garcia JF, Ott M, Hannsmann ML, Berger F, Hummel M, Davi F, Bruggemann M, Lavender FL, Schuuring E, Evans PA, White H, Salles G, Groenen PJ, Gameiro P, Dongen JJ (2007) Improved reliability of lymphoma diagnostics via PCR-based clonality testing: report of the BIOMED-2 Concerted Action BHM4-CT98-3936. Leukemia 21(2):201–206. https://doi.org/10.1038/sj.leu.2404467
