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Diagnosis and treatment of marginal zone lymphoma

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Sergio Cogliatti[a]*, Mario Bargetzi[b], Francesco Bertoni[c,d], Felicitas Hitze[e], Andreas Lohri[f], Ulrich Mey[g], Alexandros Papachristofilou[h], Christian Taverna[i], Emanuele Zucca[c]*, Christoph Renner[j]*

[a] Institute of Pathology, Kantonsspital St. Gallen, Switzerland; [b] Oncology-Haematology, Kantonsspital Aarau, Switzerland; [c] IOSI Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [d] Lymphoma and Genomics Research Programme, IOR Institute of Oncology Research, Bellinzona, Switzerland; [e] Oncology-Haematology, Kantonsspital St. Gallen, Switzerland; [f] Oncology-Haematology, Kantonsspital Baselland, Liestal, Switzerland; [g] Oncology and Haematology, Kantonsspital Graubuenden, Chur, Switzerland; [h] Radio-Oncology, Universitätsspital Basel, Switzerland; [i] Oncology, Kantonsspital Münsterlingen, Switzerland; [j] Onkozentrum Hirslanden & Zürich, Zürich, Switzerland

*SC, EZ, and CR contributed equally to this manuscript

Summary

Marginal zone B-cell lymphoma (MZL) comprises three distinct entities, namely extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma), nodal MZL and splenic MZL. Although these three diseases are somewhat related by their histogenetic origins, each displays its own clinical and biological characteristics that are reflected in the individual diagnosis, therapy and outcome. The rarity and heterogeneity of MZL have greatly hampered patient management and therefore no clear guidelines are available on the optimal treatment regimens. This review discusses the main features, diagnosis and treatment of these MZL subtypes.

Key words: marginal zone lymphoma; extranodal marginal zone lymphoma; mucosa-associated lymphoid tissue; splenic marginal zone lymphoma; nodal marginal zone lymphoma; pathology; diagnosis; treatment; chemotherapy; rituximab

Introduction

The term "marginal zone B-cell lymphoma" (MZL) refers to a group of indolent B-cell lymphomas that originate from the marginal zone of lymphoid follicles [1]. The World Health Organization (WHO) classifies MZL into three distinct entities: extranodal MZL (MALT lymphoma), nodal MZL and splenic MZL [2]. Mucosa-associated lymphoid tissue (MALT) lymphoma is the most commonly occurring subtype. It can arise at almost any extranodal site and is often associated with chronic antigenic stimulation, either as a result of chronic infection (such as gastric *Helicobacter pylori* infection) or autoimmune diseases [3–6]. MALT lymphomas may be subdivided into gastric and non-gastric tumours. In a recent survey of 18 US cancer registries, MALT lymphomas comprised 5%, nodal MZL 2.4% and splenic MZL 0.7% of all B-cell lymphomas [6]. Primary nodal MZL is rare and the least understood entity, and has to be clearly distinguished from secondary nodal involvement that arises as a consequence of disseminated extranodal or splenic MZL [7].

Patients with splenic MZL typically present with enlarged spleens and involvement of the abdominal lymph nodes and bone marrow that displays a rather specific sinusoidal growth pattern. A subset of patients shows liver infiltration and leukaemic conversion with or without the presence of villous lymphocytes [7].

Abbreviations

BR:	bendamustine plus rituximab
CHOP:	cyclophosphamide, doxorubicin, vincristine and prednisone
CLL:	chronic lymphocytic leukaemia
CR:	complete response
CT:	computed tomography
DLBCL:	diffuse large B-cell lymphoma
ESMO:	European Society for Medical Oncology
^{18}F-FDG:	fluorine-18-fluorodeoxyglucose
FISH:	fluorescence *in-situ* hybridisation
FL:	follicular lymphoma
GELA:	Groupe d'Etude des Lymphomes de l'Adulte
GI:	gastrointestinal
HBV:	hepatitis B virus
HCL:	hairy cell leukaemia
HCV:	hepatitis C virus
HIV:	human immunodeficiency virus
IFN-α:	interferon α
IGHV:	immunoglobulin heavy chain variable region
LDH:	lactate dehydrogenase
LPL:	lymphoplasmacytic lymphoma
MALT:	mucosa-associated lymphoid tissue
MCL:	mantle cell lymphoma
MNDA:	myeloid cell nuclear differentiation antigen
MZL:	marginal zone lymphoma
NHL:	non-Hodgkin's lymphoma
ORR:	overall response rate
OS:	overall survival
PAS:	periodic acid-Schiff
PET:	positron emission tomography
PFS:	progression-free survival
PPI:	proton pump inhibitors
RT:	radiation therapy
SLL:	small lymphocytic lymphoma
WHO:	World Health Organization.

Although these MZL subtypes share some morphological and immunophenotypic features, their distinct biological characteristics have led to their separation into three individual entities in order to facilitate treatment. As a result of the rarity of the disease, there are only a few randomised trials testing the various treatment options and consequently very little guidance on how to manage MZL.

This review discusses the clinical features, diagnosis and management of each subtype alongside the open questions that should be considered by the physicians who treat this complex disease.

MALT lymphoma (extranodal MZL)

Clinical features and diagnosis

MALT lymphomas often arise in areas that are genuinely devoid of lymphoid tissue, usually following a period of chronic inflammation that results in the accumulation of B cells [8]. The median age at presentation is around 60 years, with a slightly higher proportion of females affected [9]. According to the 2008 WHO classification, MALT lymphoma is by definition an extranodal tumour composed of morphologically heterogeneous marginal zone B cells of varying centrocytoid, monocytoid or lymphocytoid appearance intermingled with scattered immunoblasts and centroblasts [2]. MALT lymphomas are generally indolent and have a good prognosis with 5-year overall survival (OS) rates over 85% [9]. The most common site of MALT lymphoma is the stomach (accounting for one third of cases), but the disease also occurs in the salivary glands, ocular adnexa, thyroid, lungs, breast and other tissues. The clinical features and symptoms of MALT lymphomas greatly depend on the organ of origin. Patients with gastric MALT lymphoma commonly suffer from nonspecific dyspepsia, nausea, epigastric pain and eventually from gastrointestinal bleeding.

One area of uncertainty relates to the optimal staging system that should be used for MALT lymphomas, par-
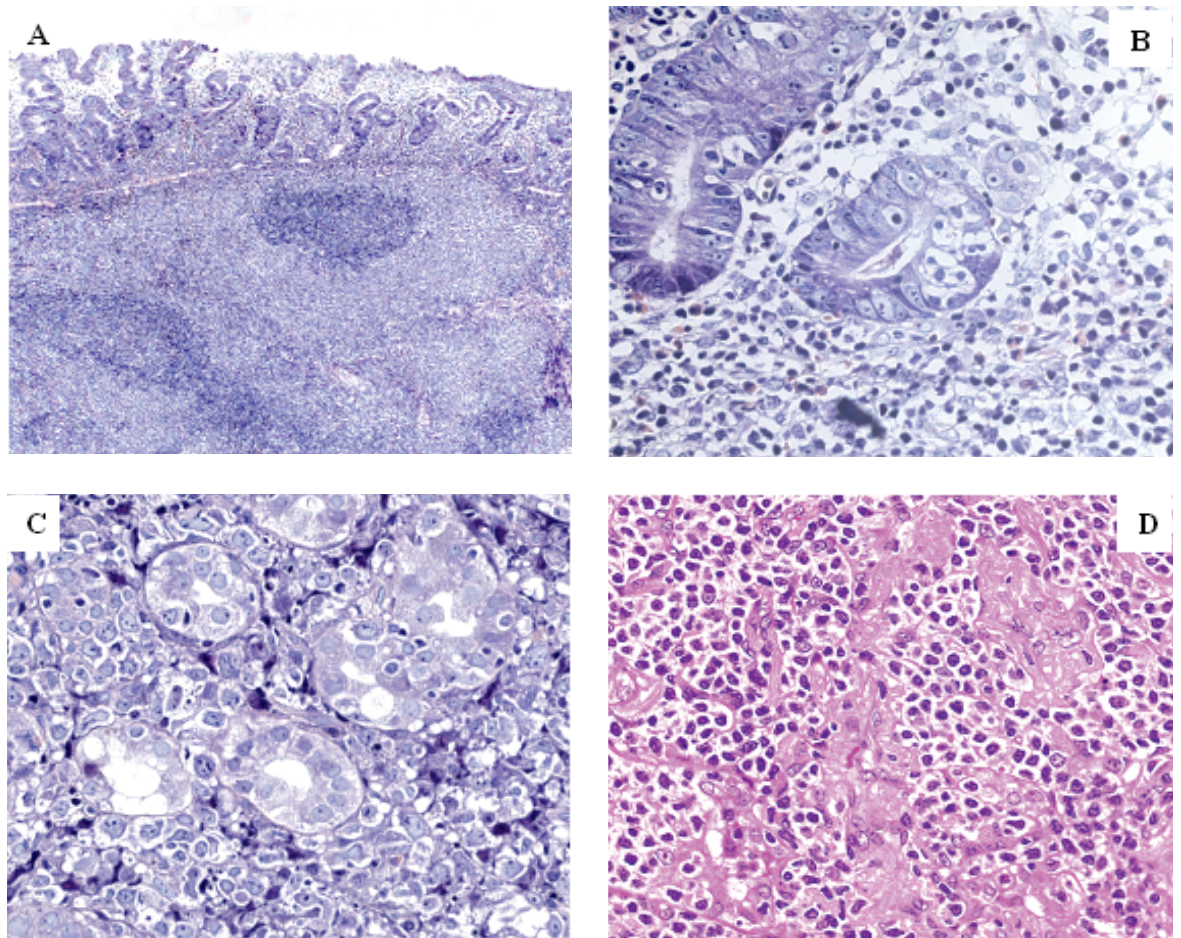
Figure 1: Representative micrographs of (mucosa associated lymphoid tissue (MALT) lymphomas. A) Low grade gastric MALT lymphoma (overview of a surgical specimen), B) low grade gastric MALT lymphoma with lymphoepithelial lesions C) high-grade blastoid gastric MALT lymphoma, and D) low grade pulmonary MALT lymphoma.

ticularly for gastric tumours. The Ann Arbor staging system has been commonly applied, although it was originally designed for use with nodal lymphomas and therefore is not fully applicable to the specific characteristics of extranodal tumours in general or gastric MALT lymphomas in particular [9]. Thus, the modified Ann Arbor system is more appropriate [10]. Due to the possibility of disease dissemination to multiple extranodal sites [11, 12], it may be challenging to detect and identify additional occult lymphoma manifestations.

Raderer et al. performed an extensive staging evaluation in 140 patients, and their findings suggested that initially advanced and disseminated disease occurs more frequently in cases where the lymphoma is not primarily localised in the gastrointestinal tract [13]. Due to the possibility of disseminated disease, a thorough work-up is recommended for all MALT lymphomas regardless of the site of presentation [14]. A recent meta-analysis of studies published up to February 2014 on the detection rate of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and PET / computed tomography (CT) showed that MALT lymphoma is a ^{18}F-FDG-avid tumour in many cases, especially in those with extra-gastric presentation, with a pooled detection rate of 71% (95% confidence interval [CI] 61–80%) [15]. These findings suggest a potential role of ^{18}F-FDG PET/CT in the initial evaluation, particularly in patients for whom radiotherapy alone is planned to treat localised disease. Diffusion-weighted magnetic resonance imaging has been recently reported to be a very valuable tool, possibly superior to CT and ^{18}F-FDG PET/CT scans in pre-therapeutic assessment and staging of MALT lymphoma [16].

Today, diagnosis of gastric MALT lymphoma is based on the histopathological evaluation of gastric biopsies [17] (fig. 1). Immunohistochemically, MALT lymphomas are typically positive for CD20 and CD79a, and negative for CD5, CD10 and CD23. They may also express CD21 and CD35. However, no specific marker exists for conclusively identifying MALT lymphomas [18]. The European Society for Medical Oncology (ESMO) clinical practice guidelines recommend endoscopy of the oesophagus, stomach and duodenum accompanied by multiple biopsies taken from each of these regions, as well as from any site with an abnormal appearance. The guidelines also recommend endoscopic ultrasound for assessment of the lymph nodes and depth of gastric wall infiltration. Special care should be taken to rule out histologically the presence of confluent sheets of transformed large B cells highlighted by an elevated proliferation rate as measured by Ki67 (MIB-1) immunoreactivity, which represent diffuse large B-cell lymphoma (DLBCL) [17]. Table 1 summarises the recommended diagnostic work-up procedures for MALT lymphoma.

Upon diagnosis of gastric MALT lymphoma, it is important to assess the presence of *H. pylori*, as this will have an impact on the subsequent therapy. *H. pylori* is a Gram-negative bacterium considered to be one of the most infectious agents in the stomach and in parts of the gastrointestinal tract, producing inflammation. Although a wide battery of tests exists for the detection of *H. pylori* (including serology, urea breath tests, faecal antigen tests, histology and cultures from biopsy samples) [19], it is noteworthy that these are not standardised and no guidelines exist as to which test(s) should be performed. A negative *H. pylori* histological status should be verified using several strategies such as the urea breath test or the stool antigen and serological tests [20–22].

Pathogenesis

There is a strong association between chronic infection/inflammation and the pathogenesis of MALT lymphoma [23, 24]. Of all these, the infectious aetiology of gastric MALT lymphoma has been the most extensively documented. *H. pylori* infection is a major causa-

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Table 1: Summary of work-up procedures for mucosa-associated lymphoid tissue (MALT) lymphomas.

All MALT lymphomas [8, 14, 17]
Clinical history and physical examination (including lymph nodes, eye, ear, nose throat, liver and spleen)
Laboratory tests
Complete blood cell count
Evaluation of liver and kidney function
Serum LDH and β2-microglobulin levels
Serological HIV, HCV and HBV testing
CT scan of the chest, abdomen and pelvis
Bone marrow biopsy
Biopsy of the affected tissue(s)
Morphological and immunophenotypic (modified Giemsa, pan-CK, CD20, CD3, MIB-1) investigations
Gastric MALT [17]
Helicobacter pylori serology and/or stool antigen test
Endoscopic ultrasound
Evaluation of *t(11;18)* /BIRC3(API2)-MALT1 [genetic evaluation is not mandatory for the initial diagnosis]
Non-gastric MALT [8, 14]
Endoscopic examinations of the gastroduodenal tract to rule out concomitant gastric involvement
Endoscopic otorhinolaryngologic examinations
MRI of the orbit
CT scan of the parotid/salivary glands

CT = computed tomography; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging

tive factor in the development of gastric MALT lymphoma, where it has been hypothesised that the lymphoma arises from *H. pylori*-stimulated B cells. Recent evidence also points towards an infectious origin for orbital MALT lymphomas, with the potential culprit being the intracellular bacterium *Chlamydia psittaci* [25, 26]. Other infectious agents that have been implicated in the pathogenesis of MZL include *Borrelia burgdorferi* (MALT lymphomas in the skin), *Campylobacter jejuni* (MALT lymphomas in the small intestine) [27] and *Achromobacter xylosoxidans* in the lung [24]. Autoimmune diseases also increase the risk of devel-

oping non-gastric MALT lymphomas [23]. Both Hashimoto thyroiditis and immune sialadenitis as part of Sjögren syndrome are characterised by the infiltration of B cells in the thyroid and salivary glands, respectively, followed by progressive lymphoproliferation [23, 28]. However, it is important to note that not all patients infected with *H. pylori*, *C. psittaci* or those with autoimmune disorders develop lymphoma, indicating that other risk factors also play a role in the development of these tumours. There is some evidence indicating that recipients of solid transplants have an increased risk of certain lymphomas (including MZL of MALT-type), suggesting a possible role for immunosuppression in the aetiology of certain lymphoma subtypes [29, 30].

Table 2: Summary of immunophenotypic and cytogenetic findings in marginal zone B-cell lymphoma (MZL) including differential diagnoses [2, 8, 9, 14, 17, 50, 51, 85].

MALT lymphomas [18, 24, 87, 89, 97]
Positive for IgM, CD20, CD79a, CD21, CD35
Negative for CD5, CD10, CD23, and cyclin D1
t(11;18) translocation in gastric MALT lymphoma in 30–50% of cases
Trisomy of chromosomes 3 and 18
Inactivation of *TNFAIP3* (6q23)
Differential diagnoses [2]:
Absence of CD5 is against MCL and SLL/CLL
Absence of cyclin D1/SOX11 is against MCL
Absence of CD10 is against FL
Nodal MZL [8, 50, 51]
Positive for CD19, CD20, CD79a and PAX5
Usually negative for CD5, CD10, and CD23
Positive for MNDA
Trisomy of chromosomes 3 and 18.
Somatic mutations of *PTPRD, NOTCH2, MLL2*
Differential diagnoses:
FL with marginal zone differentiation: Careful histological review to identify BCL2-negative centroblasts, and centrocytes positive for BCL6 and CD10. FL is often positive for GCET1, LMO2 and HGAL and shows *t(14:18)* translocations. Stathmin1 may be helpful for identifying FLs that are negative for BCL2 and/or CD10.
LPL: clinical features, LPL presents with Waldenström's macroglobulinaemia, nodal MZL presents with lymphadenopathy. Nodal MZL has monocytoid cellular morphology, marginal zone growth pattern, and follicular colonisation. MYD88 L265P mutations are more common in LPLs.
Splenic MZL [2, 44]
Positive for CD20, CD79a, co-expression of IgM/IgD
Usually negative for CD5, CD10, CD23, CD43, and CD103
Trisomy of chromosomes 3 and 18
Deletion of *7q31-q32*
Cytogenetic aberrations involving chromosome 8
Somatic mutations of *NOTCH2, KLF2, MLL2, TP53*
Frequent use of IGHV1-02
Differential diagnoses [2]:
Absence of cyclin D1/SOX11 is against MCL
Absence of CD5 is against SLL/CLL
Absence of CD103 and annexin A1 against HCL
Absence of CD10 and BCL6 is against FL

CLL = chronic lymphocytic leukaemia; FL = follicular lymphoma; LPL = lymphoplasmacytic lymphoma; MALT = mucosa-associated lymphoid tissue; MCL = mantle cell lymphoma; MNDA = myeloid cell nuclear differentiation antigen; SLL = small lymphocytic lymphoma

Cytogenetic, molecular and immunophenotypic findings

A common genetic aberration associated with gastric MALT lymphomas is *t(11,18)(q21;q21)*. This translocation results in a fusion between the *BIRC3 (API2)* gene and the *MALT1* gene, producing a chimeric protein with the ability to enhance cell survival and proliferation by apoptosis inhibition and activation of the NF-κB pathway, respectively [24, 31]. The 30–50% of patients with gastric MALT lymphoma who have this translocation are more likely to exhibit widely disseminated disease and are more likely to be *H. pylori* negative [32]. The *t(14;18)(q32;q21)* translocation involving an abnormal recombination at the *IGH* locus on chromosome 14 and the *MALT1* locus on chromosome 18 is more frequently seen in non-gastric MALT lymphomas [24, 33]. Trisomy of chromosomes 3 and 18 and inactivation of TNFAIP3 (6q23) occur frequently [18]. High levels of the FOXP1 protein (a result of chromosomal translocations or copy number changes) is also associated with poor prognosis in MALT lymphoma [34, 35]. The molecular and cytogenetic aberrations associated with the MZL entities are summarised in table 2.

Treatment

The optimal front-line treatment of patients with MALT lymphoma remains to be determined. The ESMO guidelines emphasise *H. pylori* eradication therapy for all gastric MALT lymphomas, regardless of stage [17]. The recommendation for first-line treatment is triple therapy, consisting of the use of a proton pump inhibitor (PPI) in combination with clarithromycin and amoxicillin (or metronidazole) [17]. The results from one study suggest that the presence of the *t(11;18)* translocation in patients with gastric MALT lymphoma may predict lack of response to *H. pylori* eradication therapy [32]. There is still a controversy regarding the use of

antibiotic therapy for non-gastric MALT lymphomas, excluding MALT lymphoma of the ocular adnexa, where eradication of *C. psittaci* with tetracycline has been associated with improved response rates and progression-free survival (PFS) [36, 37]. For gastric MALT lymphoma, antibiotic therapy is considered worthwhile even for *H. pylori*-negative cases, with respect to false negative testing or the presence of other *Helicobacter* species (such as *H. heilmannii* or *H. felis*) [17, 38]. There is no robust evidence-based guidance for the treatment of patients who require further therapy beyond *H. pylori* eradication or for those with non-gastric MALT lymphoma. For patients who do not respond to *H. pylori* eradication, those with early-stage gastric MALT lymphoma, or those with non-gastric MALT lymphoma, there is some data supporting the efficacy of localised radiation therapy. Disease control can be achieved by a medium dose of involved-field radiation therapy (24–30 Gy administered within a 3–4 week period is suggested by the ESMO guidelines) [17, 39, 40]. Data from several studies indicate that low-dose radiation therapy (between 2–4 Gy) is effective and well tolerated for the treatment of MALT lymphomas [41, 42], and could be particularly useful for minimising radiation-associated morbidity in certain tissues such as the ocular adnexa [41]. Immunochemotherapy and/or chemotherapy are also effective for all stages of MALT lymphomas [17]. The combination of rituximab plus various chemotherapy agents has been shown to yield good response rates [43–46]. So far, the only immunochemotherapy regimen that has been tested in a relatively large randomised study is rituximab plus chlorambucil. Results from the IELSG-19 study in patients with non-gastric MALT lymphomas and gastric MALT lymphomas refractory to prior antibiotic therapy suggested that the combination of chlorambucil plus rituximab yielded a better outcome compared with either single regimen, although it should be noted that the 5-year OS rate was similar in all three treatment arms [45]. Results from a recent phase II study by the Spanish GELTAMO group in 60 patients with MALT lymphoma (at any site, and at any stage) showed that the combination of bendamustine plus rituximab yielded good response rates [47]. At 2 years and 4 years, event-free survival rates were 93% and 88%, respectively. The ESMO guidelines suggest the use of rituximab plus chemotherapy for systemic treatment, but there is no further guidance to indicate which chemotherapy agent(s) should be used in combination with rituximab [17].

Nodal MZL

Clinical features and diagnosis

Nodal MZL is a rare entity, accounting for approximately 2% of lymphomas [6, 48, 49]. The median age at diagnosis is ~60 years; however, there is a wide age distribution. Most patients present with stage III or IV disease [50]. There is an equal prevalence in males and females. It is thought to be an indolent disease with a clinical course similar to that of follicular lymphoma (FL), but with a highly variable presentation [7]. By definition, the disease has a nodal origin showing morphological, immunophenotypic, and genetic characteristics that overlap with those of extranodal, rather than those of splenic MZL (fig. 2). Clinical features at presentation usually include peripheral lymphadenopathy often involving the head and neck region. Bone marrow involvement is seen in 30–60% of cases. Laboratory findings show elevated levels of β2-microglobulin and lactate dehydrogenase in roughly one-third of patients, and the presence of an M component (~10% of patients), although the proportions vary depending on the series [50, 51]. Since nodal MZL was only recognised and accepted as a distinct entity by the WHO classification in 2008, data on the clinical features, pathology and outcome are limited and vary considerably.

In terms of morphology, nodal MZL displays a para-, peri-, or interfollicular growth pattern in strands and sheets, which in the beginning excludes reactive lymphoid follicles. These may, however, be colonised in later disease phases. Cytologically, nodal MZL shows small to medium sized lymphoid tumour cells of monocytoid, centrocytoid, or lymphocytoid appearance, intermingled with tumour blasts in varying numbers. MZL is characterised by plasmacytoid differentiation to varying degrees and may display intranuclear PAS-positive inclusions (Dutcher bodies). In general, nodal MZL cannot be strictly distinguished from secondary lymph node involvement by primary extranodal or splenic tumours and requires full knowledge of the clinical features of these malignancies [52] (fig. 2). Morphologically, there is a significant overlap between nodal MZL and lymphoplasmacytic lymphoma (LPL). However, the latter is more typically associated with IgM-paraproteinaemia that manifests as a result of Waldenström's macroglobulinaemia, as it is characterised by the MYD88 L265P somatic mutation [53]. MZL also displays a morphological resemblance to FL, inasmuch as on the one hand MZL typically colonises reactive germinal centres mimicking FL, whereas on the other hand FL may display the feature of a marginal zone differentiation [54] (fig. 2). In cases where the tumour cells have colonised the follicle, neoplastic cells
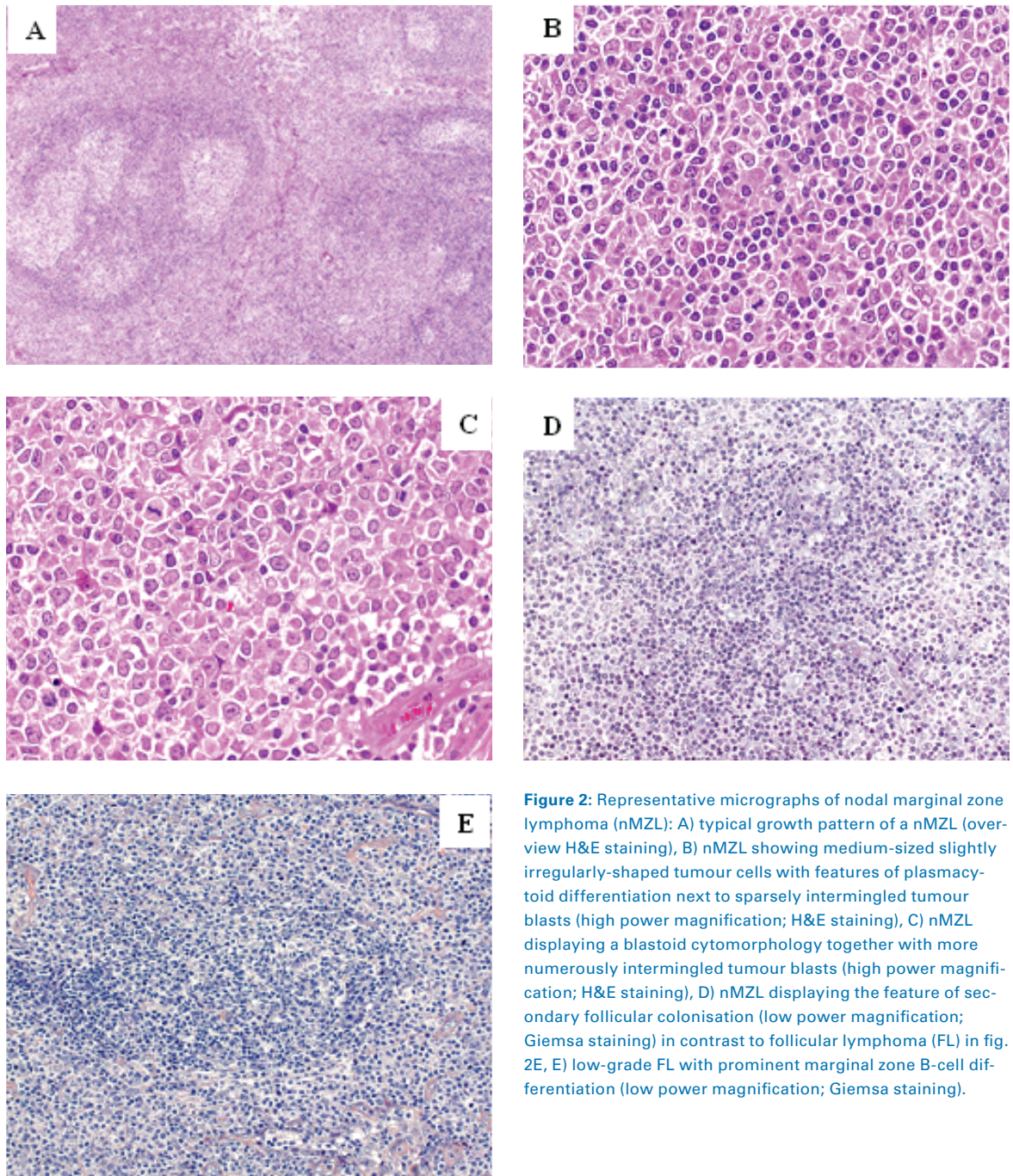
Figure 2: Representative micrographs of nodal marginal zone lymphoma (nMZL): A) typical growth pattern of a nMZL (overview H&E staining), B) nMZL showing medium-sized slightly irregularly-shaped tumour cells with features of plasmacytoid differentiation next to sparsely intermingled tumour blasts (high power magnification; H&E staining), C) nMZL displaying a blastoid cytomorphology together with more numerously intermingled tumour blasts (high power magnification; H&E staining), D) nMZL displaying the feature of secondary follicular colonisation (low power magnification; Giemsa staining) in contrast to follicular lymphoma (FL) in fig. 2E, E) low-grade FL with prominent marginal zone B-cell differentiation (low power magnification; Giemsa staining).

express BCL2 and MUM1 but are negative for BCL6 and CD10 [55]. Recently, myeloid cell nuclear differentiation antigen (MNDA) has been reported as a potential diagnostic marker that may distinguish positive nodal MZL from negative FL [56]. However in such cases FISH analysis is a more reliable tool and should be performed for the detection of *t(14;18)(q32;q21)* chromosomal translocation, a rather specific molecular marker for FL.

As for the other MZL entities, the optimal diagnostic and staging procedures remain to be defined. The staging procedures recommended by the ESMO guidelines include full blood and differential counts, complete biochemical tests for liver and kidney function, LDH, β2-microglobulin, and protein electrophoresis [57]. Bone marrow biopsies and chest/abdominal CT scanning are also part of the ESMO staging checklist. Although some reports are optimistic about the use of PET for studying the extent of the disease [58, 59], this matter is still under debate and the ESMO guidelines do not advocate the use of PET in routine staging and follow-up [57]. A summary of the work-up procedures for nodal MZL is shown in table 3.

Table 3: Summary of work-up procedures for nodal marginal zone B-cell lymphoma (MZL) [57].

Nodal MZL
History and physical examination
Bone marrow biopsy
Laboratory tests
Complete blood count
Evaluation of liver and kidney function markers
Protein electrophoresis
Calcium, LDH, albumin and β2-microglobulin levels
HCV, HBV and HIV testing
Helicobacter pylori testing in the case of gastric symptoms
CT scan of the chest, abdomen and pelvis
Gastroduodenal endoscopy plus ear, nose and throat evaluation to exclude extranodal disease

CT = computed tomography; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase

Pathogenesis

Several reports hint at an association with autoimmune disorders including rheumatoid arthritis, vitiligo, systemic lupus erythematosus, chronic thyroiditis and Sjögren's syndrome [51, 60]. Other studies have shown a high hepatitis C virus (HCV) seroprevalence amongst patients with nodal MZL [61–63]. As for the MALT lymphomas, chronic inflammation may play a role in the disease aetiology at least in some patients, but the pathogenic mechanisms of nodal MZL remain unknown.

Cytogenetic, molecular and immunophenotypic findings

It is difficult to establish a characteristic immunophenotypic or cytogenetic profile for nodal MZL. It expresses the B-cell markers CD19, CD20, CD79a and PAX5, but is usually negative for CD5, CD10, and CD23 [50;51]. IgM/IgD co-expression (a characteristic of splenic MZL) is found in only a small percentage of nodal cases and its significance is still under debate. Plasmacytic differentiation can be highlighted by expression of plasmacytic markers, such as CD38, CD138 and MUM1 [64]. The molecular and cytogenetic aberrations in nodal MZL are summarised in table 2.

The majority of patients with nodal MZL exhibit somatic mutations in the IGHV genes, which are more commonly of the IGHV3 and 5 families [65]. There are often trisomies of chromosomes 3 and 18 [2, 18, 44]. The arrival at a diagnosis of nodal MZL is usually via exclusion of other less likely diseases with overlapping features (table 2).

Treatment

There are no guidelines for the preferred treatment of nodal MZL. The ESMO guidelines recommend that patients are managed with the same strategies as for FL [57]. In patients with limited disease, localised radiation therapy can achieve good tumour control. Current recommendations support the use of a 24 Gy dose applied only to the involved disease sites [66–68]. The use of low-dose (4 Gy) radiation therapy has shown good results in the palliative treatment setting [69, 70]. In advanced stages of the disease, immunochemotherapy is the main treatment option [57]. A recent study in patients with indolent and mantle cell lymphomas (MCL) (including a subset of patients with nodal MZL) tested rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) versus bendamustine plus rituximab (BR) [71]. The data showed that BR yielded similar outcomes to R-CHOP in terms of PFS, but BR was preferable because it was less toxic [71]. However, owing to the rarity of nodal MZL, there is no robust evidence base from which to select the optimal regimen.

Splenic MZL

Clinical features and diagnosis

Splenic MZL accounts for <2% of all lymphomas, but is the most common lymphoma originating in the spleen [6, 72]. The median age at presentation is around 65 years with equal incidence in both genders. Splenic MZL is believed to be indolent. Median OS is >10 years but around one third of patients have more aggressive disease, resulting in a shorter OS (4 years). In ~5% of patients, the disease undergoes transformation into large B-cell lymphoma. The tumour consists mainly of small lymphoid cells. It originates in the marginal zone within the white pulp of the spleen and may secondarily involve splenic hilar lymph nodes and bone marrow, where it may show a typical and rather specific sinusoidal pattern (fig. 3). The liver is also a frequent site of secondary involvement [72]. Some patients may become leukaemic but no peripheral lymphadenopathy is found [2]. Most patients are asymptomatic and their disease discovered incidentally as anaemia and/or thrombocytopenia in a routine blood count [72]. On the other hand, splenomegaly can be detected upon clinical examination, sometimes accompanied by anaemia, autoimmune thrombocytopenia and variably by villous lymphocytes in peripheral blood [2, 44]. The main clinical symptoms in patients with advanced disease are due to splenomegaly (abdominal discomfort or pain, cytopenias).

As for the other MZL entities, arrival at a correct diagnosis of splenic MZL requires the integration of clini-
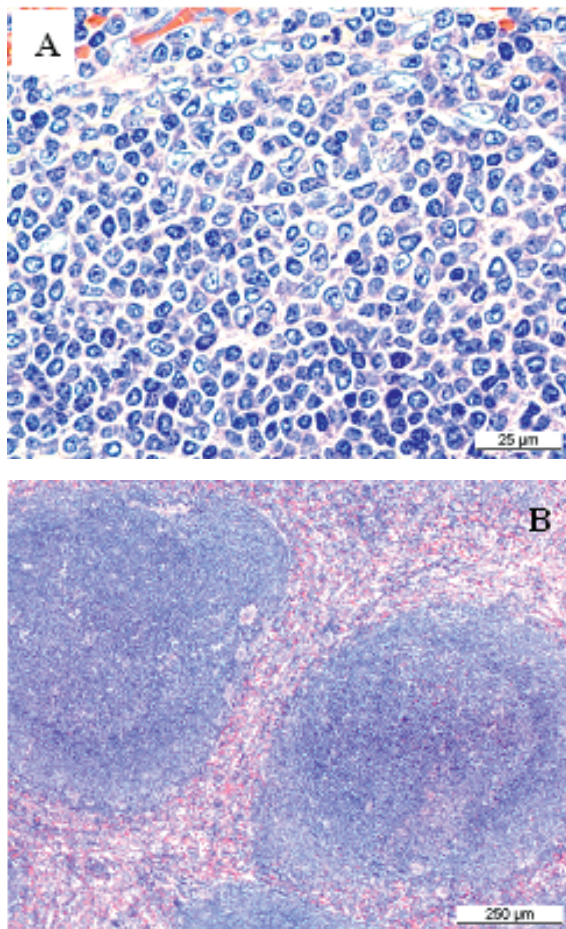
Figure 3: Representative micrographs of splenic marginal zone lymphoma (MZL). A) Splenic MZL and B) splenic MZL with low-magnification view of the growth pattern.

cal, laboratory, imaging and pathological data (table 2 and table 4). However, a diagnosis of splenic MZL no longer strictly requires splenectomy [57] since characteristic features that allow a diagnosis based on bone marrow examination and peripheral blood flow cy-

Table 4: Summary of work-up procedures for splenic marginal zone B-cell lymphoma (MZL) [72].

Splenic MZL
History and physical examination (particularly spleen)
Spleen histology
Bone marrow biopsy
Laboratory tests
Complete blood cell count
Evaluation of liver and kidney markers
Serum LDH, albumin and β2-microglobulin levels
HCV, HBV and HIV testing
Screening for autoimmunity
CT scan of the chest, abdomen and pelvis

CT = computed tomography; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase

tometry have recently been established [73, 74]. The tumour cells are positive for cell surface IgM, CD20 and CD79a. They are usually negative for CD5, CD10, CD23 and CD43. It is important to distinguish splenic MZL from hairy cell leukaemia (HCL); in this case, the absence of CD103 and (even more specifically) of annexin A1 weighs against a diagnosis of HCL [75] (table 2). Histology plays a pivotal role in the diagnostic procedure for splenic MZL (table 2 and table 4). Screening for HCV is important to identify those patients who may benefit from antiviral therapy [72]. As for non-splenic MZL, the patient's hepatitis B virus (HBV) and human immunodeficiency virus (HIV) status should also be tested. Complete medical history, physical examination, full blood counts, renal and liver biochemical tests, and serum levels of lactate dehydrogenase (LDH) and β2-microglobulin should be performed [73]. Autoimmune diseases are found in 10–15% of patients, and thus should be taken into special consideration [76].

Anaemia, thrombocytopenia, the presence of extrahilar lymphadenopathy, elevated LDH and reduced albumin levels are the main clinical prognostic factors that can be used for risk stratification [76–78]. Tumour infiltration of non-haematopoietic tissues is also an unfavourable prognostic factor [41].

Pathogenesis

The aetiology is unknown but chronic antigen stimulation is possibly a trigger for disease onset [79, 80]. In circumscribed populations such as those in southern Italy and parts of the US, splenic MZL occurs more frequently in HCV carriers and eradication of the virus results in lymphoma remission [81–84], comparable to the effect of *H. pylori* eradication in gastric MALT lymphoma.

Cytogenetic, molecular and immunophenotypic findings

Pathophysiologically, splenic MZL has yet no known specific genetic marker [85]. The most frequently encountered cytogenetic abnormalities are trisomy of chromosomes 3 and 18, and deletion at 7q31.31–q32.3, with the latter considered typical of splenic MZL [18, 86]. Somatic mutations of *KLF2* and of genes involved in the Notch and NF-κB pathways are frequent events [87–89]. Other aberrations have also been reported (table 2), but these are not present in all patients.

About half of patients have somatic mutations in the IGHV genes, and there is a biased usage of IGHV1-2 and IGHV3-23 [79, 86]. A large case series recently indicated that one third of splenic MZL patients carry the IGHV1-02 gene, with a strong bias (90% of cases) towards involvement of the allele 04 polymorphic variant [79],

suggesting a selection by antigenic stimulation and/or an origin from progenitor cells that are adapted to particular antigenic challenges through selection of specific VH domains [79].

Treatment

There are no treatment recommendations for splenic MZL. Because the disease is believed to be indolent, a watch and wait strategy appears to be feasible in many cases. There is no evidence that early intervention would favour patients with only mild splenomegaly and no systemic symptoms [72], except for HCV-positive patients, who may benefit even more from an early onset of antiviral therapy [90]. However, one open question is whether patients with a poor prognostic profile should not receive earlier treatment. The ESMO guidelines list the criteria indicative for starting treatment, namely: progressive splenomegaly, progressive cytopenias, decrease of haemoglobin <10 g/dl, platelet count <80 000/µl, and neutrophil count <1000/µl [57]. There are several possible treatment strategies. Splenectomy has been a traditional first-line option which can alleviate splenomegaly-related symptoms and improve cytopenias in the majority of patients, resulting in a median PFS of 5 years [91]. However, removal of the spleen will not influence bone marrow or peripheral blood involvement [92]. Chemotherapy or immunochemotherapy regimens may be proposed for patients who are unable or unwilling to undergo splenectomy. Chemotherapy regimens are

based on alkylating agents such as chlorambucil or cyclophosphamide [44]. Single-agent fludarabine has also been used with some success, although the data come from case series with small patient numbers [93, 94]. Rituximab, alone or in combination with chemotherapy, also achieves high overall and complete response rates. The ESMO guidelines suggest the use of four weekly doses of rituximab at 375 mg/m^2 as a first-line alternative to splenectomy, although the optimal treatment regimen and long-term outcome still needs to be established [57].

Follow-up for all MZL entities

Follow-up of non-gastric MALT disease should proceed in the same manner as for other indolent lymphomas (table 5). For *H. pylori*-positive gastric MALT lymphoma patients, eradication of *H. pylori* cannot be conclusively confirmed earlier than 6 weeks after antibiotic treatment [17]. Endoscopic examinations and a harvest of multiple biopsies 3–6 months after completion of antibacterial treatment should follow to exclude potential residuals [95]. Histological evaluation of repeated biopsies remains an essential part of the follow-up procedure. It should be noted that the interpretation of post-treatment lymphoid infiltrates in gastric biopsies is a challenge [17]. ESMO guidelines recommend that new biopsies should be compared to previous biopsies using the Groupe d'Etude des Lymphomes de l'Adulte (GELA) scoring system [96]. The same procedure of endoscopy plus biopsies should be performed at least twice a year for another 2 years after treatment to monitor stable lymphoma regression. Although it is possible to encounter transient local relapses upon histological examination, these are usually self-limiting, particularly when there is no *H. pylori* re-infection [57]. Another open question is for how long these patients should be followed up. For the time being, the ESMO guidelines state that in the long run, all gastric MALT lymphoma patients should be re-evaluated clinically and endoscopically every 12-18 months. It should be noted that patients with gastric MALT lymphoma have a reported six-fold higher risk of gastric adenocarcinoma compared with the general population [57].

For patients with splenic or nodal MZL who are asymptomatic, monitoring should be performed every 6 months (table 5). The follow-up procedures should be done more frequently (every 4–6 weeks in the first 3 months) in patients who have undergone treatment. Clinicians and pathologists performing the follow-up on all MZL entities should keep a watchful eye for potential high grade tumour transformation.

Table 5: Summary of follow-up and monitoring procedures for the marginal zone B-cell lymphoma (MZL) entities [57].

MALT (non-gastric and gastric)
Complete clinical examination (at completion of treatment)
Laboratory work-up (at completion of treatment)
Radiological or ultrasound examinations (at completion of treatment)
Biopsy of any remaining lesions (at completion of treatment)
Clinical and endoscopic follow-up every 12–18 months
Gastric MALT
After antibiotic treatment, test for eradication of *Helicobacter pylori* (stool antigen test, breath test)
Endoscopic follow-up with biopsies (2–3 months after treatment, then twice a year for the next 2 years)
Splenic and nodal MZL
Complete clinical examination
Blood counts
Laboratory work-up
– For asymptomatic patients, every 6 months
– For treated patients, at the end of treatment, 4–6 weeks during the first 3 months, then every 6 months

MALT = mucosa-associated lymphoid tissue

Conclusions

MZL lymphomas are rare and in the majority of cases they have an indolent clinical course. The extranodal, nodal, and splenic subtypes share some overlapping features but nevertheless represent individual entities. Because of their rarity, there are not many randomised trials evaluating therapeutic options, nor guidelines or protocols for the treatment and follow-up of these patients. Treatment decisions should be a result of collaboration between the clinician, the pathologist and the patient.

Correspondence:
Professor Dr. med.
Christoph Renner,
Onkozentrum Hirslanden,
Witellikerstrasse 40,
CH-8038 Zürich
Christoph.Renner[at]
hirslanden.ch

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