B-cell malignancies - A new knowledge hub on the latest research in therapeutic advances

EDUCATIONAL CONTENT AVAILABLE ON THE HUB:

- On-demand Webinars - earn CME credit
- Infographics
- Patient Case Studies
- Currated Research Articles

...and much more

VISIT KNOWLEDGE HUB TODAY

This educational resource has been supported by Eli Lilly.

WILEY

Received: 28 March 2023 | Accepted: 28 March 2023

DOI: 10.1002/hon.3152

WILEY

REVIEW ARTICLE

Marginal zone lymphomas

Emanuele Zucca[1,2,3] | Davide Rossi[1,2,3] | Francesco Bertoni[1,2,3]

[1]Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland

[2]Institute of Oncology Research (IOR), Bellinzona, Switzerland

[3]Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland

Correspondence
Emanuele Zucca, Institute of Oncology Research, IELSG, Via Francesco Chiesa 5, Bellinzona 6500, Switzerland.
Email: emanuele.zucca@eoc.ch

Abstract

The three main types of marginal zone lymphoma (MZL), recognized by the current lymphoma classifications are the extranodal MZL of mucosa-associated lymphoid tissue, the splenic MZL, and the nodal MZL. They share some karyotype lesions (trisomies of chromosomes 3 and 18, deletions at 6q23), and alterations of the nuclear factor kappa B (NFkB) pathway are also common in all of them. However, they differ in the presence of recurrent translocations, mutations affecting the Notch signaling pathway (NOTCH2 and less commonly NOTCH1), the transcription factors Kruppel-like factor 2 (KLF2) or the receptor-type protein tyrosine phosphatase delta (PTPRD). This review summarizes the most recent and significant advances in our understanding of the epidemiology, genetics, and biology of MZLs and outlines the current principles of the standard management of MZL at different anatomic sites.

KEYWORDS
extranodal MZL of MALT type, marginal zone lymphoma, nodal MZL, splenic MZL

1 | DEFINITION

Marginal zone B-cell-derived lymphoproliferative diseases encompass extranodal marginal zone lymphoma (MZL) of mucosa-associated lymphoid tissue (MALT lymphoma), splenic MZL, and nodal MZL. Variants include pediatric subtype of nodal MZL and immunoproliferative small intestinal disease (IPSID), a form of MALT lymphoma. Clonal B-cell lymphocytosis of marginal-zone origin may precede the development of an overt MZL.[1]

In 2022, two updated lymphoma classifications were proposed, the International Consensus Classification (ICC) and the 5th edition of the World Health Organization (WHO) classification, both derived from the previous WHO classification.[2,3] The ICC and the 5th edition of the WHO classification are largely superimposable for MZLs (see Table 1). The main difference from the prior taxonomy relates to the distinction of marginal zone cutaneous lymphomas as a distinct entity separate from other MALT lymphomas. Due to their indolent behavior, the ICC characterizes these cutaneous forms as primary cutaneous marginal zone "lymphoproliferative disorders" rather than "lymphomas," and they typically do not require aggressive treatment. The ICC distinguishes two subtypes of them based on expression of class-switched IgG or IgM.[2]

Marginal zone B-cells, responding to both T-cell-dependent and T-cell-independent antigens,[4,5] are considered the normal counterparts of the neoplastic cells in all subtypes of MZLs.[6]

These lymphomas infiltrate the marginal zone of reactive B-cell follicles and spreads into the interfollicular region. In epithelial tissues, the neoplastic cells commonly infiltrate the epithelium and form lymphoepithelial lesions. MZL B-cells are morphologically heterogeneous, including centrocyte-like marginal zone B-cells monocytoid cells, small lymphocytes, and occasional large cells reminiscent of immunoblasts and centroblasts. The degree of plasma cell differentiation varies.[7–9] MZLs represent distinct clinicopathological entities with specific diagnostic criteria, genetic features, and clinical behaviors, although their differential diagnosis

TABLE 1 Marginal zone lymphoma entities across recent classifying proposals.

ICC, 2022	WHO-5th, 2022	Revised WHO-4th, 2016
Splenic MZL	Splenic MZL	Splenic MZL
Extranodal MZL of mucosa-associated lymphoid tissue, also known as MALT lymphoma	Extranodal MZL of mucosa-associated lymphoid tissue, also known as MALT lymphoma	Extranodal MZL of mucosa-associated lymphoid tissue, also known as MALT lymphoma
Primary cutaneous marginal zone lymphoproliferative disorder (*new distinct entity*)	Primary cutaneous marginal zone lymphoma (new distinct entity)	Not considered as an entity
Nodal MZL	Nodal MZL	Nodal MZL
Pediatric nodal MZL (*provisional*)	Pediatric nodal MZL (*distinct entity*)	Pediatric nodal MZL (*provisional*)

Abbreviations: ICC, International Consensus Classification; MZL, marginal zone lymphoma; WHO, World Health Organization Classification of Tumors of the Haematopoietic and Lymphoid Tissues.

is challenging, particularly in cases with disseminated disease involving lymph nodes, spleen, peripheral blood, bone marrow, or other extranodal sites.[1]

2 | EPIDEMIOLOGY AND RISK FACTORS

MZLs are a subtype of B-cell non-Hodgkin lymphomas (NHL) and are the third most common non-Hodgkin lymphoma (after diffuse large B-cell lymphoma and follicular lymphoma). In 2016, approx. 7500 new cases of MZL were diagnosed in the United States, accounting for 7% of all mature NHLs. The age-standardized incidence rate of MZL was 19.6 per 1,000,000 person-years, as reported by the US SEER-18 program from 2001 to 2017.[10]

Among MZL subtypes, 9% were splenic MZL, 30% nodal MZL, and 61% extranodal MZL. The incidence of MZL has increased by 1.0% annually from 2001 to 2017 in the United States, with similar trends reported in other countries, likely due to improved diagnosis. The incidence of MZL subtypes appears to be changing over time, with an increase in splenic MZL and a decrease in extranodal MZL.[10–14]

There are several recognized risk factors for MZL, including *Helicobacter pylori* infection, a family history of NHL, certain autoimmune diseases (such as Sjögren syndrome and systemic lupus erythematosus), and genetic loci in the human leukocyte antigen (HLA) region. There is also evidence linking MZL to a number of other factors, including *Chlamydia psittaci*, *Borrelia burgdorferi*, hepatitis C virus (HCV), human immunodeficiency virus, and solid organ transplantation.[10,15–17] The decrease in gastric MZL observed in western countries is believed to be due to reduced *H. pylori* infection, wider indications for *H. pylori*-eradication therapy, and increased over-the-counter use of proton pump inhibitors.[1,6]

3 | MOLECULAR PATHOGENESIS

Chronic antigenic stimulation is a fundamental characteristic of MZL development. Histological features of extranodal MZL, such as the presence of tumor lymphocytes in non-neoplastic follicles, scattered transformed blasts, prominent plasma cell differentiation, and a rich T-cell non-neoplastic component, suggest involvement in an immune response. Extranodal MZL commonly arises in mucosal sites where the presence of lymphocytes is acquired in response to chronic infectious conditions or autoimmune processes. The tumor cells in MZLs show somatic hypermutation and intraclonal variation of the variable region of the immunoglobulin heavy chain (IGHV) genes and are driven by direct antigen stimulation. Antibodies expressed by MZL cells are often self-directed, indicating cross-reactivity between exogenous and endogenous antigens. Over time, abnormal B-cell clones with successive genetic abnormalities can replace the normal B-cell population of the inflammatory tissue, resulting in lymphoma.

Nuclear factor kappa B pathway activation (NF-kB), trisomies of chromosomes 3 and 18, and mutations in chromatin remodeling gene proteins are common in all MZLs. Extranodal MZLs have recurrent chromosomal translocations, with t(11; 18)(q21; q21), t(14; 18)(q32; q21), and t(1; 14)(p22; q32) being the most common. Deletions at 7q31–32 are a typical characteristic of splenic MZL. The Notch pathway, which regulates normal B-cell differentiation and homing, is also activated by genetic events in MZLs. Mutations of NOTCH2 gene are recurrent in splenic and nodal MZLs, while mutations in NOTCH1 are less common in splenic MZLs. Inactivation of protein tyrosine phosphatase delta (PRPRD) is almost exclusively detected in nodal MZLs.[6,18,19]

A recent study identified two genetic clusters in splenic MZL: NNK (comprising ~60% of SMZL and characterized by mutations of NF-κB, NOTCH and KLF2) and DMT (~30% of cases, harboring mutations affecting DNA damage response, MAPK and TLR). NNK-SMZLs have inferior survival compared to DMT-SMZLs. Mutations in genes coding for epigenetic regulators, such as KMT2D and CREBBP, are common in all MZLs and highlight the deregulation of the epigenome in these types of lymphomas.[20]

4 | TREATMENT

The course of MZLs is generally indolent, particularly in patients with extranodal MZLs. Median survivals exceed 10 years, even though the disease affects the patient's life expectancy. Active surveillance is

recommended for patients with advanced stage disease who are asymptomatic as the disease does not impair survival.[21] *H. pylori* should be eradicated in all patients with gastric MZL and *H. pylori* infection, irrespective of the stage. The anti-*H. pylori* regimen should be chosen based on the regional microbial patterns of antibiotic resistance. In localized, *H. pylori*-positive gastric MZLs, the initial treatment should solely be *H. pylori* eradication, which induces lymphoma regression and long-term clinical disease control in three-quarters of patients. Post-antibiotic follow-up studies have shown a frequent persistence of monoclonal B-cells after histological regression of the lymphoma as well as transient molecular or histological relapses without clinical or endoscopic evidence of disease; these patients can safely be managed with a watchful waiting strategy. Patients with concomitant chronic HCV infection should have the hepatitis treated and cured, because sustained MZL regression are observes in two thirds of patients after hepatitis treatment with direct-acting antivirals agents.[22]

The efficacy of antibiotic therapy for non-gastric extranodal MZLs is unproven. There is controversy regarding the use of antibiotics directed against *C. psittaci* for treatment of ocular adnexa MZLs, as they have shown variable activities. Immunoproliferative small intestinal disease may respond to antibiotics against *Campylobacter jejuni*.[23]

In *H. pylori*-negative gastric MZLs, antibiotic treatment is likely ineffective, but it can still lead to occasional lymphoma responses, possibly due to false-negative results of microbiological tests or infection by other micro-organisms. Involved-site radiotherapy (24 Gy) is extremely efficacious in patients with localized *H. pylori*-negative gastric MZL or in those without lymphoma regression following antibiotic therapy, as well as in localized, non-gastric extranodal MZLs, leading to long-term local control in about 90% of patients. Long-term complications may include xerostomia after parotid irradiation, hypothyroidism after thyroid irradiation, cataracts and dry eyes after orbital irradiation.[24] Dose de-escalation to 4 Gy reduces toxicities but its use outside palliative indications is controversial. The addition of adjuvant chemotherapy to radiotherapy does not translate into better cure rates.[22]

Advanced stage MZLs are not curable with conventional treatment. While remissions can be attained, repeated relapses are common. Treatment focuses on symptoms alleviation and quality of life improvement. Asymptomatic patients may be managed expectantly (watchful waiting). Patients with advanced stage extranodal and nodal MZL often have, however, high tumor burden that require treatment. The criteria for initiating treatment in splenic MZLs include progressive or symptomatic splenomegaly and/or any progressive cytopenia.

Symptomatic, advanced stage MZLs are best treated with rituximab-based approaches. In the absence of clear survival advantages, combination immunochemotherapy may be preferred over rituximab alone for patients with severely symptomatic or bulky disease, and for those who place a high value on a longer treatment-free period. The chemotherapy backbone (e.g., chlorambucil or bendamustine) may be selected according to patient age, fitness and organ functions since older/frail adults receiving bendamustine-rituximab have shown higher rates of fatal toxicities. The need for rituximab maintenance is controversial in MZLs, with no evidence of survival benefit.

Historically splenectomy has been the recommended first treatment for patients with splenic MZL, since it also allows for a definitive pathologic diagnosis. Splenectomy can have however, severe complications (including infections, bleeding, thrombosis, and long-term immune-deficiency against capsuled bacteria) and in the last 2 decades, splenectomy has been progressively replaced by rituximab (with or without chemotherapy) as the preferred initial therapy.[21,22,25]

The progression or relapse of the disease should be documented with a biopsy and a shift to an aggressive lymphoma should be considered in certain cases such as asymmetric growth and uptake in PET scans, systemic symptoms, and elevated LDH. There are no specific phase 3 trials of relapsed MZL, but there are small phase 2 trials and a few FDA-approved treatments. The management is highly individualized and depends on various factors such as the stage of the disease, previous treatments, and patient age and health. Second-line and subsequent treatments may include rituximab, lenalidomide plus rituximab, ibrutinib, or copanlisib. Patients with MZL transformation to an aggressive lymphoma can be treated with anthracycline-based chemoimmunotherapy, transplantation with autologous stem cells, or immunotherapy with CAR-T cells.[1]

ACKNOWLEDGEMENT

Open access funding provided by Universita della Svizzera italiana.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

REFERENCES

1. Rossi D, Bertoni F, Zucca E. Marginal-zone lymphomas. *N Engl J Med*. 2022;386(6):568-581. https://doi.org/10.1056/nejmra2102568
2. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. *Blood*. 2022;140(11):1229-1253. https://doi.org/10.1182/blood.2022015851
3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. *Leukemia*. 2022;36(7):1720-1748. https://doi.org/10.1038/s41375-022-01620-2
4. Palm A.-KE, Kleinau S. Marginal zone B cells: from housekeeping function to autoimmunity? *J Autoimmun*. 2021;119:102627. https://doi.org/10.1016/j.jaut.2021.102627
5. Song H, Cerny J. Functional heterogeneity of marginal zone B cells revealed by their ability to generate both early antibody-forming cells and germinal centers with hypermutation and memory in response to a T-dependent antigen. *J Exp Med*. 2003;198(12):1923-1935. https://doi.org/10.1084/jem.20031498
6. Bertoni F, Rossi D, Raderer M, Zucca E. Marginal zone lymphomas. *Cancer J*. 2020;26(4):336-347. https://doi.org/10.1097/ppo.0000000000000463
7. Campo E, Pileri SA, Jaffe ES, Nathwani HK, Müller-Hermelink HK. Nodal marginal zone B-cell lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of*

Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC; 2017:263-265.
8. Cook JR, Isaacson PG, Chott A, et al. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. IARC; 2017:259-262.
9. Piris MA, Isaacson PI, Swerdlow SH, et al. Splenic marginal zone lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Revised 4th ed. IARC Press; 2017:223-225.
10. Cerhan JR, Habermann TM. Epidemiology of marginal zone lymphoma. *Ann Lymphoma*. 2021;5:1. https://doi.org/10.21037/aol-20-28
11. Bastos-Oreiro M, Muntanola A, Panizo C, et al. RELINF: prospective epidemiological registry of lymphoid neoplasms in Spain. A project from the GELTAMO group. *Ann Hematol*. 2020;99(4):799-808. https://doi.org/10.1007/s00277-020-03918-6
12. Luminari S, Merli M, Rattotti S, et al. Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study. *Blood*. 2019;134(10):798-801. https://doi.org/10.1182/blood.2019001088
13. Smith A, Crouch S, Lax S, et al. Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network. *Br J Cancer*. 2015;112(9):1575-1584. https://doi.org/10.1038/bjc.2015.94
14. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin*. 2016;66(6):443-459. https://doi.org/10.3322/caac.21357
15. Vannata B, Pirosa MC, Bertoni F, Rossi D, Zucca E. Bacterial infection-driven lymphomagenesis. *Curr Opin Oncol*. 2022;34(5):454-463. https://doi.org/10.1097/cco.0000000000000886
16. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. *Blood*. 2016;127(17):2082-2092. https://doi.org/10.1182/blood-2015-12-624304
17. Zucca E, Bertoni F, Vannata B, Cavalli F. Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. *Clin Cancer Res*. 2014;20(20):5207-5216. https://doi.org/10.1158/1078-0432.ccr-14-0496
18. Cascione L, Rinaldi A, Bruscaggin A, et al. Novel insights into the genetics and epigenetics of MALT lymphoma unveiled by next generation sequencing analyses. *Haematologica*. 2019;104(12):e558-e561. https://doi.org/10.3324/haematol.2018.214957
19. Cheah CY, Zucca E, Rossi D, Habermann TM. Marginal zone lymphoma: present status and future perspectives. *Haematologica*. 2022;107(1):35-43. https://doi.org/10.3324/haematol.2021.278755
20. Bonfiglio F, Bruscaggin A, Guidetti F, et al. Genetic and phenotypic attributes of splenic marginal zone lymphoma. *Blood*. 2022;139(5):732-747. https://doi.org/10.1002/hon.43_2879
21. Florindez JA, Alderuccio JP, Reis IM, Lossos IS. Splenic marginal zone lymphoma: a US population-based survival analysis (1999–2016). *Cancer*. 2020;126(21):4706-4716. https://doi.org/10.1002/cncr.33117
22. Zucca E, Arcaini L, Buske C, et al. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(1):17-29. https://doi.org/10.1016/j.annonc.2019.10.010
23. Lecuit M, Abachin E, Martin A, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. *N Engl J Med*. 2004;350(3):239-248. https://doi.org/10.1056/nejmoa031887
24. Teckie S, Qi S, Chelius M, et al. Long-term outcome of 487 patients with early-stage extra-nodal marginal zone lymphoma. *Ann Oncol*. 2017;28(5):1064-1069. https://doi.org/10.1093/annonc/mdx025
25. Iannitto E, Bellei M, Amorim S, et al. Efficacy of bendamustine and rituximab in splenic marginal zone lymphoma: results from the phase II BRISMA/IELSG36 study. *Br J Haematol*. 2018;183(5):755-765. https://doi.org/10.1111/bjh.15641

How to cite this article: Zucca E, Rossi D, Bertoni F. Marginal zone lymphomas. *Hematol Oncol*. 2023;41(S1):88-91. https://doi.org/10.1002/hon.3152