

## MARGINAL-ZONE LYMPHOMAS

### *Epidemiology*

Marginal-zone lymphomas (MZL) comprise extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), also known as MALT lymphoma, splenic MZL (SMZL) with or without villous lymphocytes and nodal MZL (NMZL). MZLs represent approximately 5%–15% of all non-Hodgkin lymphomas in the Western world. EMZLs comprise approximately two-thirds and can arise at any extranodal site, usually in the context of chronic antigenic stimulation due either to infections or autoimmune disorders. The stomach is the most common site, followed by ocular adnexa, lung and salivary glands. SMZL accounts for ~20% and NMZL for <10% of cases.

### *Signs and symptoms*

NMZL is usually discovered when a patient has a swollen, painless lymph node in neck, armpits, or groin. Patients with SMZL typically present with symptoms related to splenomegaly (abdominal discomfort or pain in left areas of abdomen). Patients with EMZL may present with a variety of signs and symptoms related to the extranodal site involved by lymphoma, including symptoms of gastritis for gastric EMZL. Moreover, patients with MZL may sometimes experience symptoms like: loss of weight, fever, night sweats, abdominal bloating or pain, fatigue.

### *Diagnosis and risk stratification*

the diagnosis of NMZL should be based on a surgical specimen/excisional lymph node biopsy. The diagnosis of EMZL relies on biopsy of involved extranodal site, for instance on gastroscopy for gastric EMZL. The diagnosis of SMZL may be based on splenectomy (spleen histology). However, in most instances, it may be established through a combination of peripheral blood/bone marrow aspirate morphology and flow cytometry, as well as bone marrow biopsy histology and IHC, reviewed by expert hematopathologists/hematologists.

For NMZL and EMZL initial work-up should include a bone marrow aspirate and biopsy and a computed tomography (CT) scan of the neck, thorax and abdomen and a positron emission tomography (PET)–CT scan. SMZL is usually FDG not avid and only a CT scan of the neck, thorax and abdomen is required for the staging. There are some variables that have prognostic relevance: age, stage, number of nodal areas involved by lymphoma, bone marrow involvement, LDH levels, hemoglobin and platelet levels, early progression within 24 months from diagnosis.

### *Treatment*

Treatment of MZL depends on the subtype, on the involved site and on the stage. NMZL is generally managed similarly to FL (radiotherapy in localized disease, immunochemotherapy in advanced, high tumor-burden disease, without rituximab maintenance). Helicobacter Pylori (HP)-positive gastric EMZL is initially treated with antibiotics-based eradication treatment alone, which results in complete response in 65% of cases. More advanced or HP eradicating therapy-resistant cases should be treated with radiotherapy or immunochemotherapy. A similar approach is usually pursued in Chlamydia Psittaci-positive ocular adnexa EMZL, which are initially managed with doxycycline therapy alone. Other EMZL are usually managed by involved-site radiotherapy in localized stages and by immunochemotherapy (usually rituximab-bendamustine) in advanced stages. Symptomatic SMZL cases may be managed in selected cases (minimal bone marrow involvement, no lymph node enlargement, cytopenias) with splenectomy, although in most cases the current treatment relies on

rituximab monotherapy or immunochemotherapy (usually rituximab-bendamustine. Our treatment approach is based on International guidelines (i.e. ESMO [doi.org/10.1093/annonc/mdx223](https://doi.org/10.1093/annonc/mdx223)). In case of relapsed or refractory disease, there are many treatment options, including alternative immuno-chemotherapy regimens, autologous stem cells transplantation in young patients, targeted therapies like Bruton tyrosin-kinase inhibitors (i.e. Ibrutinib). In our center, patients with unsatisfactory responses to standard therapy can be evaluated for clinical trials. For more information about the hematologic trials available in Varese, please visit the section "Trial Unit" of the Institutional website (<https://www.asst-settelaghi.it/ematologia>).