Splenic marginal zone lymphoma (SMZL)

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Continuous research and targeted examinations of blood and bone marrow result in various diagnostic recommendations for patients with splenic marginal zone lymphoma (SMZL).

**Diagnostic recommendation**

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Definition and characteristics of SMZL

The splenic marginal zone lymphoma (SMZL) belongs to the group of marginal zone lymphomas and is a rare mature B-cell neoplasm with indolent clinical course. The annual incidence is 0.13/100,000 persons (Liu et al. 2013). The disease occurs median in the 6th decade of life and manifests itself in the spleen with frequent involvement of bone marrow and peripheral blood. The splenic marginal zone lymphoma is formed by B cells from the marginal zone of the white splenic pulp (Swerdlow et al. 2017).

The aetiology of the splenic marginal zone lymphoma is not clear, but immunological stimulation seems to play a role besides acquired pathogenic mutations in oncogenes and tumor suppressor genes. Epidemiological studies also point to a connection to viral infections with human herpes virus 8 and hepatitis C virus (HCV) (Benavente et al. 2011, Hermine et al. 2002).

Classification of splenic marginal zone lymphoma

The group of marginal zone lymphomas accounts for up to 9% of non-Hodgkin’s lymphomas (The non-Hodgkin’s lymphoma classification project 1997). Based on the localization of the primary tumor, the WHO classification (2017) distinguishes three entities:

- Splenic marginal zone lymphoma (SMZL)
- Extrancoval marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma (NMZL) and the subtype of paediatric nodal marginal zone lymphoma

All three entities have the indolent course and the associated favorable prognosis in common.

SMZL - Diagnostics

Cytomorphology

The cytomorphology and histology of blood, bone marrow and lymph nodes is a guiding principle in the diagnostics of the various lymphoma entities for the control of the downstream diagnostics. On the one hand, the assessment of the bone marrow smear allows a first important statement to be made as to whether lymphoma circulation or lymphoma infiltration exists or is possible. Cytomorphology and histology are also useful for assessing the degree of lymphocyte maturity.

Cytomorphologically, lymphatic cells with short, polar arranged villi, plasmocytoid lymphatic cells and inconspicuous lymphocytes can be detected in peripheral blood smears. Morphological differentiation from other lymphoma entities is usually not easy (Haferlach 2020).

Immunophenotyping

Immunophenotyping in lymphomas allows to clearly determine the line affiliation to the T- or B-line. Furthermore, multiparametric flow cytometry is often indispensable to distinguish a reactive alteration from a lymphoid neoplasm, e.g. in EBV infections.

The neoplastic cells express the B-cell antigens CD19, CD20, CD22, CD79a and CD79b. Frequently there is an expression of membrane-bound immunoglobulin (mostly IgM, more rarely IgD) and FMC7. Usually CD5, CD10 and CD103 are not expressed. In rare cases, however, an expression of CD5 may occur, which is not associated with an altered prognosis (Baseggio et al. 2010). Since CD5 is an important marker to differentiate splenic marginal zone lymphoma from other lymphoid entities such as chronic lymphocytic leukemia or mantle cell lymphoma, it must also be assessed by morphological and genetic parameters. The antigens CD11c, CD23, CD25, CD43 and cyclin D1 can be variably expressed. In contrast to mantle cell lymphoma, cyclin D1 is only weakly expressed in splenic marginal zone lymphoma and can serve for differentiation (Arcaini et al. 2016, Pisil et al. 2017).

Table 1: Immunophenotyping of splenic marginal zone lymphoma
### Chromosome analysis

Up to 80% of patients with splenic marginal zone lymphoma have an aberrant karyotype (Zinzani 2012), with half of these patients having a complex aberrant karyotype (Saldia et al. 2010). Various numerical and structural chromosomal abnormalities are found, none of which is specific to the SMZL.

The most common chromosomal alteration in splenic marginal zone lymphoma is 7q deletion, which is present in 39% of cases with aberrant karyotype and only rarely in other mature B cell neoplasms. In addition to the 7q deletion, trisomy 3 or a gain of 3q is observed in about 25% of cases. Further abnormalities are gains of 1q, 8q, 12q, or 18 and/or losses of 1p, 6q, 8p or 13q. In about 12% of the cases a translocation involving the ICH locus (14q32) is present (Salido et al. 2010).

In very rare cases of splenic marginal zone lymphoma, the translocation t(2;7)(p12;q21); CDK6/IGK is present, which activates the CDK6 gene (Brito-Babapulle et al. 2002).

Cytogenetic abnormalities in splenic marginal zone lymphoma

**Gains:**
- 1q, 3q, 8q, 12q, 18

**Losses:**
- 1p, 6q, 9q, 8p, 13q

**Balanced translocations:**
- t(1;4)(q32)
- t(2;7)(p12;q21)/CDK6-IGK

**FISH**

Since splenic marginal zone lymphoma is characterized precisely by the absence of characteristic translocations, as is the case with follicular lymphoma (t(14;18); IGH-BCL2), mantle cell lymphoma (t(11;14); IGH-CCND1) and MALT lymphoma (t(11;18); BIRC3/MALT1, t(14;18); IGH/MALT1 or t(1;14); IGH/IgL), chromosome analysis as well as fluorescence in situ hybridization can significantly help to differentiate the presence of phenotypically similar entities of lymphomas. The presence of a 7q deletion may also indicate the presence of splenic marginal zone lymphoma.

### Molecular genetics

In a splenic marginal zone lymphoma, the most frequently mutated genes are KLF2 (21%), NOTCH2 (20%), TP53 (15%) and IGLL5 (14%). Mutations in the three gene pairs KLF2 and IGLL5, TP53 and NOTCH2, and TP53 and KLF2 rarely occur together, indicating the possible presence of genetic subtypes of the SMZL (Oquendo et al. 2019). Especially in patients with splenic marginal zone lymphoma mutations of the NFκB signaling pathway occur frequently. Besides the transcription factor KLF2, other recurrently mutated genes of the NFκB signaling pathway are: TNFAIP3 (33%), MYD88 (8%), TRAF3 (8%), CARD11 (5%), IKKβ (6%) and BIRC2 (4%) (Oquendo et al. 2019, Parry et al. 2015, Cipson et al. 2015). Furthermore, about
The splenic marginal zone lymphoma is an indolent disease. The prognosis is usually very good and the median survival is 10 years. However, in 5-10% of the patients a transformation into a large B-cell lymphoma occurs, especially into a diffuse large B-cell lymphoma (Xing et al., 2015). The prognosis for patients with transformed SMZL is adverse (Florindez et al., 2019).

In splenic marginal zone lymphoma, a prognostic score has not yet been established. The splenic marginal zone lymphoma study group is striving for risk stratification, and its prognostic index takes the following parameters into account: haemoglobin, platelet count, lactate dehydrogenase, extrahilar lymphadenopathy (Kalpadakis et al., 2014). The Intergruppo Italiano Linformi Index (IIL) also includes the clinical parameters of haemoglobin and lactate dehydrogenase, and the IIL also includes serum albumin (Arcaini et al., 2006). Mutations of the TP53 gene are associated with a worse prognosis and patients with mutations of NOTCH2 and KLF2 have been observed to require earlier treatment (Parry et al., 2015).

**Splenic marginal zone lymphoma - Recommendation**

According to the current guideline of the “European Society for Medical Oncology” (ESMO) on marginal zone lymphoma, the diagnosis of splenic marginal zone lymphoma requires besides the collection of clinical and laboratory parameters a cytomorphological and immunophenotypical analysis of peripheral blood and bone marrow aspirate as well as a histological and immunohistochemical examination of the bone marrow. In a small percentage of cases, splenectomy is necessary for the diagnosis or exclusion of a splenic diffuse small cell B-cell lymphoma of the red pulp (SDRPL) (Zucca et al., 2020).

Therapy is usually initiated if progressive or symptomatic splenomegaly is present and/or any progressive cytopenia is detectable (haemoglobin <10 g/dl, platelets <80,000/ul, neutrophils <1000/µl) (Zucca et al., 2020). The assessment of the therapy response requires, like the diagnosis, the interaction of methods of cytology, immunophenotyping as well as histology and immunohistochemistry. Thus, in addition to the clinical parameter of spleen size, hematological recovery, the proportion of circulating clonal cells in the blood and the extent of bone marrow infiltration are assessed (Zucca et al., 2020).

**References**

You can find the corresponding references here: