Nodal marginal zone lymphoma (NMZL)

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Abstract

Nodal marginal zone lymphoma (NMZL) is a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL of extranodal or splenic types. Two clinicopathological forms of NMZL are recognized: adult type and pediatric-type. NMZLs show overlapping features with other types of MZL, but distinctive features as well. NMZL remains an enigmatic entity with accompanying difficulties in diagnosis and a lack of knowledge of prognosis and treatment.

Keywords
Nodal marginal zone lymphoma; Paediatric; indolent

Identity

Other names
Monocytoid B-cell lymphoma
Parafollicular B-cell lymphoma
Nodal marginal zone B-cell lymphoma

Clinics and pathology

Disease

Nodal marginal zone lymphoma (NMZL) is a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL of extranodal or splenic types, but without evidence of extranodal or splenic disease. Presence of a primary extranodal MZL should be ruled out since approximately one third of the cases presenting as NMZL represent nodal dissemination of a MALT lymphoma.

NMZL can also be diagnosed in children, which has distinct clinical and morphological features with an excellent prognosis (Swerdlow, et al, 2008. Swerdlow, et al, 2016).

Phenotype/cell stem origin

The postulated normal counterpart of NMZL is post-germinal centre marginal zone B-cell (Swerdlow, et al, 2008). NMZL expresses pan-B-cell markers with CD43 coexpression in 50% of the cases. CD5, CD23, CD10, bcl6 and cyclinD1 are negative and bcl2 is positive in most cases.


Epidemiology

NMZL comprises only 1.5-1.8% of all lymphoid neoplasms. The reported incidence ranges from 5.7/1,000,000 person-years to 8.3/1,000,000 person-years, and steadily increased by 25% during 2001-2005 and 2006-2009 (Khalil, et al. 2014, Tadmor, et al, 2017). Most cases occur in adults with a median age around 60 years and a similar proportion in males and females.

**Clinics**

Most patients present with asymptomatic, localized or generalized peripheral lymphadenopathy. The sites of involvement are peripheral lymph nodes, occasionally bone marrow and peripheral blood (Swerdlow, et al., 2008, Swerdlow, et al., 2016). Elevated LDH (lactate dehydrogenase) levels are indicative of a less favorable prognosis, and in these cases high grade transformation must be excluded (Tadmor, et al., 2017). About 20-40% of patients with NZML develop B-symptoms and performance status is overall good. A serum M-component is present in 10% of patients (Pileri, et al., 2017). Hepatitis C virus (HCV) has been reported in a subset of NMZL patients. Autoimmune diseases are associated with NMZL, including rheumatoid arthritis, vitiligo, systemic lupus erythematosus, autoimmune hemolytic anemia, chronic thyroiditis, and Sjögren's syndrome (van den Brand, et al., 2013).

**Pathology**

NMZL is frequently a diagnosis of exclusion, including reactive hyperplasia and indolent small B cell lymphoma. Morphologically, the tumor cells surround reactive follicles and expand into the interfollicular areas. Follicular colonization may be present. In cases with a diffuse pattern, follicle remnants may be detected with stains for follicular dendritic cells and germinal centre markers. The tumour cells are composed of variable numbers of marginal zone (centrocyte-like and monocytoid) B-cells, plasma cells and scattered transformed B-cells. Diagnosis of transformation requires the identification of sheets of large cells. Plasma cell differentiation may be prominent and the differential diagnosis with lymphoplasmyctoma may be difficult. The presence of remnants of follicular dendritic meshworks suggestive of colonized follicles would favour the diagnosis of NMZL.

In paediatric NMZL, the tumor is similar to that seen in adults except that there are often progressively transformed germinal centers in which the outer border of the follicles is disrupted and infiltrated by tumor cells (Swerdlow, et al., 2008, Swerdlow, et al., 2016).

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Figure 1. Nodal marginal zone lymphoma. At low magnification, nodular growth pattern with pale cell can be seen (HE staining).
Figure 2. The tumor cells are small to medium in size, with pale cytoplasm (HE staining)

Figure 3. The tumor cells are small to medium in size, with small nucleoli in some cells (HE staining)
Figure 4. The cells are positive for CD20.

Figure 5. The proliferation index of Ki67 is low in tumor cells, with residual germinal centers.
### Treatment

Until now the clinical approach has in fact been adapted from those applied and one recommended for other indolent lymphomas. In NMZL, treatment is not always required in asymptomatic patients NMZL and like with other low grade lymphomas, a “watch and wait” policy may well be a reasonable option. In symptomatic patients requiring treatment, the therapeutic approach will differ based on whether the disease is localized or more systemic. For localized disease, surgery followed by radiotherapy is a possible option (Tadmor, et al, 2017). Targeted therapies against deregulated molecular pathways are an attractive field of investigation, but definitive data about this approach are not yet available. The research includes B-cell receptor, JAK/STAT, NF-kB, NOTCH, and Toll-like receptor signaling pathways, as well as intracellular processes such as the cell cycle, chromatin remodeling, and transcriptional regulation in terms of epigenetic modifiers, histones, or transcriptional co-repressors, along with immune escape via T-cell-mediated tumor surveillance (Pileri et al, 2017, Thieblemont et al, 2016). Bendamustine plus rituximab was found to be an active and well-tolerated regimen leading to the rapid control of disease (Laribi, et al, 2017).

### Prognosis

60-80% of the patients survive longer than 5 years. The prognosis of these patients may be predicted using the follicular lymphoma international prognostic index (FLIPI). Other prognostic values for NMZL include age >60 years, the presence of B-symptoms, elevated LDH, levels, and cyclin expression. The mean 5-year OS in published series is 62-90% (Swerdlow, et al, 2008. Swerdlow, et al, 2016, Tadmor, et al, 2017).


### Cytogenetics

**Note**

The immunoglobulin genes are clonally rearranged with a predominance of mutated VH3 and VH4 families. Trisomies 3, 18 and 7 have been observed. The translocations associated with extranodal MZL are not detected (Swerdlow, et al, 2008. Swerdlow, et al, 2016).

Unique chromosomal abnormalities including monosomy 20 and add(10)(p11.2) can be seen in a paediatric case (Aqil, et al, 2015).

Gene expression profiling analysis has demonstrated an increased expression of NFkB related genes. Some genetic defects in NMZL have been reported, including KMT2B (MLL2), PTPRD, NOTCH2, and KLF2. With the exception of MLL2, which is present in more than one third of cases, the other affected genes occur in about 20% of cases. NMZL harbored PTPRD lesions as an overmarker for this lymphoma across mature B-cell tumors, and support the distinction of NMZL as an independent clinicopathologic entity within the current lymphoma classification (Pileri, et al, 2017).

### References


This article should be referenced as such: