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# Nodal marginal zone lymphoma: Clinical features, diagnosis, management and treatment

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A B S T R A C T

Nodular marginal zone lymphoma (NMZL) is a small B-cell lymphoma involving only lymph nodes and is the least common form of MZL constituting about 10% of cases. Patients usually present with advanced disease which must be distinguished from extranodal MZL with lymph node spread. NMZL shares cytological and immunophenotypic features with MALT and splenic MZL, but has a less favorable prognosis than these two categories. It occurs mostly in adults and pediatric cases are rare. Different therapeutic approaches have been used in NMZL, but because of the small patient numbers involved, more definitive treatment is still anticipated. Recent studies suggest that it probably represents a separate entity within the broader indolent lymphoma category. In NMZL there is an emerging need to utilize novel agents, already available for indolent lymphomas. Prospective studies are required to evaluate their therapeutic efficacy for NMZL in the future.



## Introduction and some historical background

The WHO classification recognizes three different sub categories of marginal zone lymphomas (MZL): marginal zone lymphoma of mucosa-associated lymphoid tissue (MZL-MALT), splenic marginal zone lymphoma (SMZL) and nodal marginal zone lymphoma (NMZL) [1,2]. Although there is some degree of overlap in patho-biology and genetic features, these three subtypes, display different clinical patterns and vary in prognosis [1]. NMZL differs from the other two categories essentially because of the absence of extranodal involvement. It represents a primary nodal disease of small B- lymphocytes that replace and expand the marginal zone of the lymphoid follicles, in a pattern resembling that seen in lymph nodes infiltrated by MALT-type MZL [3,4].

The first three cases were described in 1986 by Sheibani et al. who first proposed the term “monocytoid B-cell lymphoma” [5]. Three years later, Piris and co-workers, reported a case of monocytoid B-cell lymphoma composed of cells with a monoclonal IgM-kappa phenotype, distinct from other B-cell subpopulations, suggesting a possible relationship to the lymphocytes of the nodal marginal zone [6]. Following the above descriptions this entity was included in the international classification of lymphomas; first in the Kiel classification in 1990 as “nodal monocytoid B-cell lymphoma,” and later in 1994, in the Revised European–American Classification of Lymphoid Neoplasms (REAL), termed “nodal marginal zone lymphoma

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with or without monocytoid B-cells" [7]. Thereafter in 2001 the WHO recognized it as a separate entity related to cells of the marginal zone, preferring the term "nodal marginal zone lymphoma", which replaced the previous designation of monocytoid B-cell lymphoma [1].

In this review we focus on the clinical features, diagnosis, and therapy of this unique entity: nodal MZL.

## Epidemiology

Nodal marginal zone B-cell lymphoma (NMZL) is a relatively rare indolent lymphoma, accounting for 1–2% of all lymphoid neoplasms, and about 10% of all MZL, thus representing the least common subtype of MZL.

The reported incidence varies in the different series, ranging from 5.7/1,000,000 person-years [8] to 8. 3/1,000,000 person-years [9], and steadily increased by 25% during 2001–2005 and 2006–2009 [8].

The median age at diagnosis is 59 years [8] and in terms of ethnicity, it has been reported to be slightly more frequent in non − Hispanic whites compared to blacks, with an incidence rate ratio of 0.65. In terms of gender, data are unequivocal, but in a recent publication based on a large patient cohort taken from SEER data: Extranodal MZL occurred equally among men and women, whereas NMZL predominated in males (male-to-female (M: F) IRR = 1; 1.5) [8].

NMZL can also be diagnosed in children, where it has distinct clinical and morphological features with an excellent prognosis [10]. Pediatric NMZL will be discussed in more detail in the section below.

## Clinical features

Given the rarity of NMZL, descriptions of clinical features are essentially based on very few reports which deal with relatively small numbers of patients [11,12]. Patients with NMZL basically have the same clinical presentation as those with indolent nodal lymphomas such as small lymphocytic and follicular lymphoma [12]. The vast majority of cases present in advanced stage which is usually non-bulky [12,13]. The disease is initially localized in peripheral lymph nodes, most frequently in the cervical region. Peripheral blood involvement is observed in only a small proportion of patients while MZL cell infiltration can be found in the bone marrow in about a third of the cases.

Association with autoimmune disease has been reported, as well as co-existence with other rare entities like Rosai-Dorfman disease, which is characterized by giant lymphadenopathy and sinus histiocytosis on histopathology [14,15].

The "interlymph Non-Hodgkin Lymphoma Subtypes Project which evaluated risk factors for the development of lymphoma [16]" has recently published pooled data collected from 1052 MZL cases including 157 patients with NMZL; Some disorders involving "B-cell activation" as well as systemic lupus erythematosus (SLE) were seen to be associated with NMZL with an odds ratio (OR) of 9.24 and 6.6 respectively. These B-cell activating diseases included Hashimoto thyroiditis, hemolytic anemia, myasthenia gravis, pernicious anemia, rheumatoid arthritis, Sjögren's syndrome.

It is noteworthy that in contrast to previous observations [17], describing an association with hepatitis C virus (HCV) and MZL in general and NMZL in particular, there appeared to be no increased incidence of HCV [16]. However in this respect we should take into account that this is still unclear as other studies have also identified an association between HCV and MZL lymphomas including NMZL [17–19]. It is indeed possible that this s association may also be dependent on geographic and/or some genetic backgrounds as most of these observations were derived from reports from Italy and Asia.

The presence of a monoclonal IgM spike is not a rare laboratory finding in NMZL and this finding always raises a possible differential diagnosis with lymphoplasmacytic lymphoma [20]. Elevated LDH (lactate dehydrogenase) levels are indicative of a less favorable prognosis, and in these cases high grade transformation must be excluded [21]. In this respect, transformation to diffuse large B-cell lymphoma has been also described in NMZL and may occur in 15% of patients after a median of 4.5 years from diagnosis [22–24].

In terms of outcome and survival: The clinical outcome of NMZL patients is similar to that of other nodal indolent lymphomas. The mean 5-year OS in published series is 62–90%.

## Pediatric NMZL

In the most recent WHO classification of tumors of hematologic and lymphoid tissues "pediatric NMZL" is described as a separate variant [1]. It has a distinct morphology and clinical presentation with a typical indolent clinical course but a much better overall prognosis than NMZL in adults [25].

In children, a male predominance is observed and most cases are asymptomatic with localized (stage I) disease, low relapse rates and an excellent outcome. In addition, there are fewer genetic aberrations than in adult NMZL [25,26]. The Children's Oncology Group for Rare and Cutaneous non-Hodgkin lymphomas (NHL) registry reported that irrespective of the different treatment approaches used, (observation alone, surgical resection, chemotherapy, radiotherapy, steroids, antibiotics, and rituximab), overall survival remains 100%, suggesting that both MZL in general as well as NMZL are curable in children (Protocol ANHL 04B1) [27].

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