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“Pediatric” Nodal Marginal Zone Lymphoma in Adults

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Abstract

Pediatric nodal marginal zone lymphoma (NMZL) is described as a separate variant of NMZL in the most recent WHO classification of tumors of hematologic and lymphoid tissues. It has distinctive morphology and clinical presentation and stands out as an indolent disease with remarkably better overall prognosis compared to classic NMZL. Here we report two adult cases of NMZL with clinical and morphologic features consistent with pediatric NMZL (pNMZL) and review available literature describing the clinical and histologic presentation of pNMZL. Two men, ages 44 and 18 years, each presented with localized cervical lymphadenopathy that histologically demonstrated florid proliferation of the marginal zone and disruption of reactive germinal centers, progressive transformation of germinal centers (PTGC) -like morphologic features typical for pNMZL and clonal disease with immunophenotype consistent with NMZL. This is the first report of pNMZL in a middle-aged person. Distinct histologic features and characteristic benign clinical course will help to distinguish this rare variant from other NMZL in adults. Clinically, recognition is important to understand the true incidence of this rare form in the adult population and to avoid unnecessary overtreatment of this indolent form.

Keywords

lymphoma; lymphoid malignancies; marginal zone lymphoma; B cell; pediatric malignancy; adult

INTRODUCTION

Nodal marginal zone lymphoma in the pediatric population (pNMZL) has been recognized in the recently updated WHO lymphoma classification as a distinct variant of nodal marginal zone lymphoma (NMZL) [1]. It comprises distinctive clinical and morphological features and has excellent overall prognosis.

Classic nodal marginal zone lymphoma (cNMZL) is well described as a relatively uncommon distinct entity within the group of marginal zone lymphomas (MZLs) having a slight female predominance, median age at presentation 60 years, relatively short median time to progression (defined from onset of treatment to the date of first progression) of approximately 15 months and median overall survival (OS) of around 5 to 6 years [2–6]. In contrast, the pediatric variant of NMZL (pNMZL) stands out as a more indolent disease having a striking male preponderance in children and young adults with a localized presentation predominantly involving cervical lymph nodes. Prolonged unmaintained remissions follow excision of the affected lymph node with, or more commonly without, additional therapy [1]. To date, the description of the pNMZL variant has been limited to a

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few reports predominantly focused on pathology. Due to the terminology as a pediatric disease and the previous focus on pathology, there is a paucity of information addressing clinical aspects of pNMZL, its manifestation, course and management, especially in adults. The true incidence of pNMZL in the pediatric population is elusive, while its frequency in the adult population is completely unknown.

Here we report two cases of NMZL in adults with clinical and morphologic features consistent with pNMZL. We also review available literature describing the clinical and histologic presentation of pNMZL in the pediatric population, as well as in adults.

PATIENTS AND METHODS

Two adult patients were diagnosed and followed at Fox Chase Cancer Center. A 44 year old man with history of Raynaud's phenomenon presented with an enlarged submental lymph node which he had noticed about 5 months earlier. He denied any constitutional symptoms and was otherwise healthy. He underwent excisional lymph node biopsy that showed total effacement of the lymph node architecture by an atypical proliferation of lymphocytes with marked marginal zone expansion resembling progressive transformation of germinal centers (PTGC) (Fig 1). The infiltrate was composed of small to medium size cells with slightly irregular nuclei and scant cytoplasm. Scattered residual germinal centers were noted with attenuated mantle zone and with evidence of colonization by the atypical cells. Flow cytometry of the lymph node revealed a monotypic lambda light chain population of B cells positive for: CD19, CD10 (dim), CD20, IgM and negative for CD5, CD23 and FMC7. The small lymphocytes appeared polytypic for kappa and lambda immunoglobulin light chains. Cytogenetics of the lymph node revealed an extra chromosome 15 in 2 of 20 metaphases. The lymph node sample was negative for Epstein-Barr viral (EBV) antigens by in situ hybridization. Staging studies including CT scan of chest, abdomen and pelvis detected no additional nodal or extranodal disease. Bone marrow biopsy revealed trilineage hematopoiesis which was negative for lymphoma by morphology and flow cytometry, and cytogenetics showed normal male karyotype. Laboratory data revealed white blood cell count (WBC) of $5.8 \times 10^3/\text{ul}$ with normal differential, hemoglobin 12.7 gm/dL, MCV 97, platelet count $197 \times 10^3/\text{uL}$. Comprehensive metabolic panel including lactate dehydrogenase (LDH) was normal. After establishing the diagnosis of NMZL on the excisional lymph node biopsy, and clinical stage IA, no further therapy was administered. The patient has remained in complete clinical remission for 12 years. Of note, his Raynaud's phenomenon resolved post-node excision and has never recurred.

An 18 year old man presented with a 2×2 cm right jugulo-digastric lymph node. He was in his usual excellent health, asymptomatic and did not recall any antecedent viral or bacterial illness or dental problems or procedures. Excisional lymph node biopsy was consistent with a clonal B-cell proliferation with marginal zone expansion, suggestive of marginal zone lymphoma. Morphologically the lymph node architecture appeared partially effaced by an expansion of the marginal zone cells. Residual germinal centers had disrupted and irregular mantle zones, reminiscent of progressive transformation of germinal centers (PTGC). Flow cytometry revealed kappa light chain restricted B cells positive for CD45, CD19, CD20, FMC7, CD38 and negative for CD5 and CD23. CD10 was dim positive by flow cytometry but negative by IHC. BCL6 was negative by IHC and no BCL2 rearrangement was detected by FISH. Bone marrow biopsy was negative for lymphoma. CT of chest, abdomen and pelvis did not reveal any other sites of disease. Laboratory data revealed WBC $8.8 \times 10^3/\text{ul}$ with normal differential, hemoglobin 16.1 gm/dL, platelet count of $304 \times 10^3/\text{uL}$. Comprehensive metabolic panel including LDH was normal. Serum protein electrophoresis showed no monoclonal gammopathy. Additional studies including hepatitis A, B and C panel, HIV antibody screening, EBV antibody panel, toxoplasma IgG antibody and Lyme

disease IgG and IgM antibodies were all negative. Cytomegalovirus panel was positive for IgG and negative for IgM. After excision, he was followed expectantly and seven months later noticed a new small cervical lymph node at the base of the right neck. Excisional biopsy was again consistent with initial diagnosis of NMZL and flow cytometry revealed similar phenotype with kappa restricted B cell clone in 17% of viable lymphoid cells, CD20 positive in 100% of clonal cells. He remained asymptomatic, his disease remained limited to one cervical lymph node and his blood work including LDH remained within normal range. He was treated with four weekly infusions of rituximab at a dose of 375 mg/m² without any significant toxicities. Three years later the patient remains in complete remission.

RESULTS

Each of our two adult patients manifested with asymptomatic isolated cervical lymphadenopathy without evidence of overt antecedent infection. Each case also demonstrated clonal proliferation of B cells with florid proliferation of the marginal zone and disruption of reactive germinal centers, progressive transformation of germinal centers (PTGC)-like morphologic features and immunophenotype consistent with NMZL. In one case the karyotype of the lymph node revealed trisomy 15 in two of 20 metaphases. Initial treatment was only resection of the affected lymph node. Patient 1 has had no recurrence in 12 years after excisional biopsy. Patient 2 had a local recurrence one year later at the initial site, in concert with a prior pNMZL case report [7], was treated with reexcision followed by rituximab weekly $\times$ 4, and remains without evidence of disease 3 years later.

DISCUSSION

This is the first report of pNMZL in a middle aged person. This 44 year old man had a typical presentation, morphologic picture revealing PTGC-like changes and marked expansion of the follicular marginal zone, and his exceptionally benign clinical course is also consistent with pNMZL. In contrast, classical NMZL typically affects older individuals with median age at diagnosis around 60 years, has slight female predominance, usually manifests with advanced lymphadenopathy at the time of diagnosis, has propensity for bone marrow involvement and relatively short median overall survival of approximately 5–6 years, compared to other MZL, such as splenic MZL or MALT type which typically have much longer survival.

Pediatric NMZL is now described as a separate variant of NMZL in the most recent WHO classification of tumors of hematologic and lymphoid tissues [1]. It has distinctive morphology and clinical presentation and stands out as an indolent disease with better overall prognosis compared to classic NMZL.

The most comprehensive report on pediatric NMZL included thirty two children and young adults[7]. The median age was 16, ranging from 2 to 27 years. There was striking male to female predominance of 5.4:1. The disease was limited in 88% of the patients, preferentially affecting the head and neck area. Lymph node morphology showed significant destruction of normal lymph node architecture with obliteration of the sinuses and predominantly interfollicular distribution of the atypical cells with substantially expanded marginal zones. In 21 of 32 cases the follicular structures resembled PTGC with markedly enlarged follicles with mantle cells infiltrating the remaining germinal centers leading to fragmentation. In contrast to reactive PTGC features, the peripheral rim of the follicle was irregular due to disruption by the expanded marginal zone. The authors reported immunohistochemical findings consistent with classic NMZL and no unique markers were identified: the atypical cells were positive for CD19 and CD20, CD43 was coexpressed in 70% of cases, while CD5, CD10, CD23, and CD3 were negative. Light chain restriction by

immunohistochemistry was seen in 48% of cases, while monoclonal IgH gene rearrangement was identified in 84% of the studied cases. CD10 and BCL6 were negative in tumor cells but highlighted residual non-malignant germinal centers. BCL2 was weakly or moderately positive in 42% and p53 was negative.

Morphologic change resembling PTGC is a dominant morphologic feature of this entity, and was described in 66% of the reported cases [7]. PTGC is seen in approximately 10% of cases with asymptomatic reactive lymphadenopathy showing marked follicular hyperplasia and represent reactive polyclonal process. It is yet to be determined whether reactive PTGC may have preceded the development of clonal proliferation and progression to pNMZL. PTGC has been associated with nodular lymphocyte predominant Hodgkin's lymphoma and less frequently with classic Hodgkin's lymphoma but not with NMZL. The majority of patients with reactive lymphadenopathy and PTGC recover without any consequences [[8–10].

Karube et al. presented 6 cases from Japan of what was referred to as “floral” variant of NMZL [11]. There were 4 male and 2 female patients with the age ranging from 18 to 66 years and 5/6 patients presented with asymptomatic localized cervical or axillary lymphadenopathy. Histological picture resembled that of a PTGC with irregular and often disturbed peripheral rim of the follicles with an expanded marginal zone and enlarged ‘floral’ lymph follicles with distinct germinal centers and thick mantle zones. The CD10 positive germinal centers were partially infiltrated by CD10–/CD20+ tumor cells. CD21 staining revealed disruption of the meshwork of follicular dendritic cells by infiltrating tumor cells. EBV was undetectable in all cases. The variant was differentiated from reactive follicular hyperplasia with PTGC and from ‘floral’ variant of follicular lymphoma. The authors suggested probable overlap between clinical and morphologic presentations of some cases of ‘floral’ NMZL and pNMZL, noting however more advanced age at presentation, with 4 of 6 cases between 34 and 66 years [7,12]. This “floral” variant of NMZL and pNMZL are similar in having atypical marginal zone lymphocytic proliferation with a tendency to colonize the germinal centers. However, in the “floral” variant residual germinal centers have irregular borders and are more prominent.

pNMZL may be confused with follicular lymphoma with marginal zone differentiation (FLMZD), especially in cases of pNMZL showing marked colonization of germinal centers. FLMZD is a rare type of follicular lymphoma characterized by a prominent marginal zone surrounding and infiltrating neoplastic germinal centers. Characteristically, neoplastic cells express germinal center markers BCL6 and CD10 which are usually lacking in NMZL. CD10 was dimly expressed by flow cytometry in the monoclonal B cells in both of our cases. However, in both cases the atypical lymphoma-like proliferation was composed of CD10 negative marginal zone cells disrupting the reactive germinal centers. Unlike pNMZL, lymph nodes of FLMZD had follicular center and monocytoid/marginal zone components clonally related to each other, both components were positive for t(14;18) translocation and were light chain restricted [13,14]. In addition to t(14;18) translocation, abnormalities involving chromosome 3 were reported in FLMZD, in particular, trisomy 3 which is a frequent abnormality in classic MZL [15,16]. It is yet to be defined if pNMZL has any specific chromosomal abnormalities distinguishing this form from other low grade lymphomas. Clinical behavior of FLMZD differs from the indolent course of pNMZL as the 30 reported cases of FLMZD had significantly shorter failure free survival ($P=0.001$) and overall survival ($P=0.04$) compared to 252 patients with pure follicular lymphoma [17].

Whereas the etiology of MZL is likely diverse there is an association with chronic antigen stimulation and inflammation. However, the antigenic driving force of NMZL and/or pNMZL remains unknown. Classic NMZL as well as splenic MZL have been linked to

hepatitis C virus (HCV) in approximately 20–25% according to some reports [4,5,18]. Given the preponderance of young patients in pediatric NMZL, an association with HCV infection is unlikely, yet needs to be further addressed. pNMZL was not associated with acquired or congenital immunodeficiency in the reported cases [7,12] or in the patients presented here and there was no known association with Epstein-Barr virus in any of the studied lymph nodes. It is not clear whether the antecedent Raynaud's phenomenon in case 1 was a paraneoplastic process or was a marker for immune dysfunction predisposing to lymphoma. Given the resolution after therapy, a paraneoplastic phenomenon seems more likely.

Chronic antigenic stimulation with a microbial pathogen of *Helicobacter pylori* is linked to Mucosa associated lymphoid tissue lymphomas (MALT) of the stomach, MALT lymphomas of the thyroid are believed to be related in some cases to chronic exposure to autoantigens of Hashimoto thyroiditis and MALT lymphomas of the salivary glands are frequently associated with Sjogren syndrome. In pNMZL one would suspect as potential antigenic candidates bacterial or viral antigens with tropism to upper aerodigestive tract given its manifestation as predominantly local disease in the head and neck area. Traverse-Glehen et al. reported biased usage of Vh gene with overrepresentation of Vh1 in 13 out of 35 and Vh4 in 7 out of 14 cases in splenic MZL and NMZL, respectively suggesting distinctive antigen driven mutations in 2 different entities of MZLs [19] Analysis of Vh gene usage might be useful in pNMZL.

Thus, there is a spectrum of indolent B cell lymphomas that involve disturbed architecture of germinal centers and surrounding marginal zones. Some of these may be antigen driven. It can be difficult to determine when they have progressed from antigen-dependent oligo- or mono- clonal proliferations to independent monoclonal growth, especially given the polyclonal reactive background and residual cells.

The true incidence of this newly recognized rare variant of NMZL is unclear. The first 2 cases were described in 1997 in 2 boys who were otherwise healthy and without evidence of congenital or acquired immune deficiency [12]. Increased awareness of this clinico-pathologic entity, due to inclusion in the WHO classification and reports such as ours in non-pediatric patients, may lead to enhanced recognition, especially in adults, which will help further characterize this rare disease. Distinct histologic features and characteristic benign clinical course help distinguish this variant from other NMZL in the adult population. Clinically, recognition is important to avoid unnecessary overtreatment of this indolent form. The name pediatric NMZL may need revision if further reports confirm our observation of this variant in older individuals. With enhanced awareness of this entity, future reports of pNMZL across all age groups should improve our knowledge of this poorly understood low grade B cell lymphoma, including incidence, clinical manifestations, cytogenetic abnormalities, molecular studies and overall prognosis to define its place within MZLs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Histologic appearance of the lymph node biopsy of patient #1. (A) Lymph node showing marked architectural effacement by marginal zone cells expansion (continuous arrow) and residual follicles (dashed arrow) (H&E, 40 $\times$). (B) PTGC-like changes seen in the expanded residual follicles (H&E, 40 $\times$). (C) Close up of the marginal zone infiltrate showing mostly small to medium size cells with slightly irregular nuclei and scant cytoplasm. Residual germinal centers are noted with attenuated mantle zone and evidence of colonization by the atypical cells (arrow) (H&E, 100 $\times$ and 400 $\times$ insert). (D) Flow cytometry showing a monotypic lambda light chain subpopulation of B cells (circled population; gating on larger lymphocytes). X axis represents staining with anti-human lambda light chain monoclonal antibody and Y axis represents staining with anti-human CD19 monoclonal antibody.