Paediatric marginal zone lymphoma and hyperplasia

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Abstract

Marginal zone lymphomas (MZL) are low-grade B-cell lymphomas arising from post-germinal memory B-cells occurring in adults with a slight female predilection. They are sub-categorized into nodal (NMZL), extra-nodal/mucosa-associated lymphoid tissue (MALT) and splenic (SMZL). MALT lymphomas are the most common (70%) followed by SMZL (20%) and NMZL (10%). Histologic transformation into aggressive B-cell lymphoma can rarely occur. MZL is extremely uncommon in the paediatric population and unlike in adults, is predominantly nodal. Paediatric NMZL (pNMZL) is an indolent, low-grade lymphoma with unique clinical and morphologic features. In contrast paediatric MALT lymphoma and SMZL are extremely uncommon and resemble their adult counterparts. Paediatric marginal zone lymphomas must be differentiated from paediatric-type follicular lymphoma (PFL) and marginal zone hyperplasia (MZH) of lymph nodes and mucosa-associated lymphoid tissue. This review summarizes the pathogenesis, morphology, genetic features of paediatric MZL and marginal zone hyperplasia. Recognition of these entities is important to avoid unnecessary therapy.

Keywords 18; atypical marginal zone hyperplasia; haemophilus influenzae; MALT lymphoma; paediatric marginal zone lymphoma; paediatric marginal zone hyperplasia; progressive transformation of germinal centers; trisomy 3

Introduction

Marginal zone lymphomas (MZL) are low-grade B-cell lymphomas arising from the post-germinal center memory B-cell. Based on their anatomic location, they are sub-categorized into extra-nodal/mucosa-associated lymphoid tissue (MALT) type, splenic (SMZL) and nodal (NMZL).[1] MALT lymphomas are the most common subtype (70%) followed by SMZL (20%) and NMZL (10%). MZL is predominantly a disease of adults with a median age ranging from 50 to 65 years with a slight female predilection.[2] The initiating event in the pathogenesis of most MZL is considered to be prolonged antigenic stimulation (including auto-antigens). This leads to polyclonal B-cell proliferation, development of secondary genetic aberrations and subsequent neoplastic transformation. The list of microbial pathogens implicated in MZL pathogenesis includes bacteria such as *Helicobacter pylori*, *Helicobacter heilmannii* (gastric), *Chlamydia psittaci* (orbital), *Campylobacter jejuni* (immunoproliferative small intestinal disease, IPSID), *Borrelia burgdorferi* (cutaneous) and viruses such as Hepatitis C virus (SMZL, NMZL). In addition, auto-immune diseases are associated with increased risk of MZL including Sjogren's disease (salivary gland), Hashimoto's disease (thyroid), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). MZL share some morphologic, immunophenotypic and recurrent genetic aberrations, including gains of whole or long arms of chromosomes 3 and 18. MZL also have subtype-specific genetic and molecular aberrations including translocations involving *IGH*, *MALT1*, *BIRC3*, *BCL10*, *FOXP1* (MALT), 7q32 deletions and NOTCH2 mutations (SMZL). Recurrent genetic aberrations unique to NMZL are not yet described. All MZL subtypes have a risk of histologic transformation to aggressive B-cell lymphoma, albeit at rates lower than that for follicular lymphoma.[3]

MZL occurring in the paediatric age group is rare. While all three subtypes have been reported, NMZL, unlike in adults are the most common subtype in children accounting for the majority of the cases (65%).[4] In a large cohort of paediatric B-cell lymphomas, MALT lymphomas comprised less than 1% of cases.[5] While extranodal MZL in children show features similar to those seen in the adults, paediatric NMZL (pNMZL) has unique clinical and morphologic features. Paediatric MZL must be distinguished from atypical marginal zone hyperplasia, often seen extranodally, which shows overlapping morphologic and immunophenotypic features.

Paediatric nodal marginal zone lymphoma (pNMZL)

Paediatric nodal marginal zone lymphoma (pNMZL) shows a striking male predominance with a greater than 10:1 ratio. Patients invariably present with isolated lymphadenopathy of the head and neck region, especially the cervical chain often noticed due to cosmetic reasons.[4] B-symptoms are uncommon and the duration of lymphadenopathy is variable. The vast majority has low-stage disease, with rare patients presenting with diffuse lymphadenopathy. Bone marrow involvement, however, has not yet been reported.[4,6]

The specific aetiology(ies) of pNMZL is unknown. In the largest series described to date, none of the patients had a history of immunodeficiency or an underlying systemic disease.[4] The increased incidence of head and neck involvement suggests a chronic antigenic stimulation through the upper aerodigestive tract. However, a recent study investigating the role of *Haemophilus influenzae* in neck lymphadenopathy did not detect this microorganism in three cases of pNMZL that were analysed.[7]

Morphologically, pNMZL shows unique features that are not identified in its adult counterpart. The nodal architecture is partially or totally effaced with attenuation of the sinuses. The marginal zones are expanded by a polymorphous infiltrate composed of small/intermediate cells with dark irregular nuclei and pale cytoplasm (monocytoid), plasmacytoid cells and rare immunoblasts. Scattered mature plasma cells are present; however, sheets of plasma cells or large immunoblasts are unusual.

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The majority of the affected follicles are expanded with fragmentation with invagination of mantle zone cells, reminiscent of progressive transformation of germinal centers (PTGC). However, unlike PTGC of reactive lymph nodes, the expanded follicles of pNMZL frequently show attenuation/absence of the mantle zones and encroaching by atypical marginal zone cells. Residual follicles are fragmented and extensive follicular colonization can be seen in a subset of cases, mimicking follicular lymphoma.

Immunophenotypically, the atypical B-cells in pNMZL show a post-germinal center phenotype. They are positive for CD20, with CD43 expression seen in most cases. They are positive for IgD in a minority of cases while CD5, CD10 and BCL6 are usually negative. Light chain restriction can be demonstrated by immunohistochemistry (IHC) in a subset of cases and is especially useful in cases with extensive follicular colonization. The proliferation index as demonstrated by Ki-67 staining is low (<10%). Epstein–Barr virus (EBV) studies are negative. In addition to immunohistochemistry (IHC), clonality can be demonstrated either by flow cytometry and/or polymerase chain reaction (PCR) analysis for immunoglobulin heavy chain (IgH) rearrangements. Representative morphologic and immunophenotypic features of pNMZL are shown in Figure 1.

Recurrent cytogenetic aberrations have been described in approximately 20% of pNMZL. Trisomy 18 is the most frequent, followed by trisomy 3.[8] Gains of chromosomes 3 and 18 are also relatively common recurrent abnormalities in NMZL in adults[9] suggesting that pNMZL have similar genetic aberrations albeit at a lower frequency.

The differential diagnosis of pNMZL includes atypical marginal zone hyperplasia (MZH), reactive hyperplasia with PTGC and paediatric follicular lymphoma (pFL). Atypical MZH can be seen in lymph nodes and MALT and will be discussed in detail below. Features favouring pNMZL over reactive hyperplasia with PTGC are the expansion of the interfollicular regions with B-cells and destruction of the majority of follicles. In addition, the attenuation of mantle zone cells (highlighted by IgD), aberrant expression of CD43 by B-cells and IGH rearrangement studies can help to confirm a diagnosis of pNMZL. The distinction between pNMZL and pFL can be challenging, as both entities can have overlapping features. Some pFL cases can show atypical follicles with prominent marginal zone differentiation whilst pNMZL can show prominent follicular colonization. The identification of increased CD10 and BCL6-positive B-cells in the interfollicular regions favours a diagnosis of pFL[10] while the presence of CD10-negative, BCL6-negative and CD43-positive B-cells in atypical follicles favours a diagnosis of pNMZL. Additionally, the abnormal follicles in pFL contain fewer PD-1 positive T-follicular helper (T_{FH}) compared to the follicles in pNMZL.[11]

Current evidence suggests that pNMZL is an indolent process with predominantly localized, low-stage disease and without large cell transformation. In the largest series published to date, only one patient had stage III disease.[4] Although additional rare cases with widespread disease have been reported, surgical excision appears to be curative in most patients with limited disease.[12] A recent case report of NMZL in an adult patient with clinical and morphologic features of pNMZL[13] is analogous to paediatric-type follicular lymphomas (PFL) occurring in the adult population and must be recognized to prevent misdiagnosis and overtreatment.[10]

Paediatric extranodal marginal zone lymphoma (pEMZL)

Paediatric extranodal marginal zone lymphomas (pEMZL) comprise less than 1% of all paediatric lymphomas.[5] Unlike pNMZL there is no male predilection with an M:F ratio of approximately 1:1. The most common sites involved are ocular adnexa, salivary glands and skin.[4] Predisposing conditions include infections with *H. pylori* and auto-immune diseases including Sjogren's syndrome and SLE.[4] Interestingly an association with HIV-infection has been reported in a small series.[14]

Morphologically, pEMZL resemble MALT lymphomas in adults. The involved sites show a dense lymphoid infiltrate with destruction of tissue/glandular architecture by centrocytic and monocytoid cells. Lymphoepithelial lesions are not uncommon. Skin lesions are non-epidermotropic with dense perivascular and periadnexal infiltrates extending into subcutaneous tissue. Reactive follicles maybe identified, but unlike pNMZL, PTGC-like changes are only seen in a minority of cases. Conversely, plasmacytic differentiation is more common and can be prominent around epithelial structures. Scattered large immunoblasts can be seen but clusters or sheets of large cells should raise the suspicion of transformation.

The immunophenotype of pEMZL is similar to pNMZL – the B-cells are positive for CD20, CD43 (majority of cases) and negative for CD10 and BCL6. Light chain restriction by immunohistochemistry or in-situ hybridization can usually be demonstrated in the plasma cell component and is useful to confirm the diagnosis. Clonality can also be demonstrated by flow cytometry or IGH rearrangement studies. Cytogenetic aberrations have been described in 18% of pEMZL, including one case with t(14;18)(*IGH-MALT1*) translocation and another with trisomy 3.

Overall, current evidence suggests that unlike pNMZL, pEMZL are similar to those occurring in adults, including rare instances of histologic transformation.[14] This argues for a similar approach to management as in adults with complete staging, appropriate initial therapy and long-term follow up.

Marginal zone hyperplasia (MZH)

Marginal zone hyperplasia (MZH) is not uncommon in reactive lymph nodes. A spectrum of morphologic patterns has been described and must be distinguished from MZL.[15] Kojima et al described cases with extensive MZH and varying degrees of PTGC. The majority of patients had isolated cervical lymphadenopathy and showed no evidence of B-cell clonality.[16]

Attygalle et al[17] first reported six cases of marginal zone hyperplasia (AMZH) of the mucosa-associated lymphoid tissue (tonsils, appendix) occurring in children. Morphologically, the lymphoid tissues showed follicular hyperplasia with PTGC. The marginal zones were expanded by centrocyte-like cells with prominent transformed blasts and follicular colonization. Infiltration of surface epithelium was identified. Immunophenotypically, the atypical B-cells were positive for CD20, CD43, IgM, BCL-2 and negative for MUM-1. Interestingly, they were lambda light chain restricted and showed a moderately high proliferative index suggesting a clonal proliferation. However, IGH gene rearrangement studies showed no evidence of clonality and the authors referred to this entity as atypical marginal zone hyperplasia (aMZH). None of the patients were treated beyond

