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Case Report

A pediatric-type follicular lymphoma with marginal zone and monotypic intracytoplasmic plasmacytic differentiation

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ABSTRACT

Pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma are rare indolent lymphomas that are distinctive entities with excellent prognoses. We present the histopathology and the immunophenotypic, cytogenetic, and gene rearrangement findings of a unique, heretofore, unreported case of a 15-year old boy with a right-groin mass (5.5 × 4.5 × 3.5 cm) with three discrete malignant components: 1) follicular lymphoma positive for CD20, CD10, and BCL6, but negative for BCL2; by flow cytometry, 9% of the cells were kappa monotypic B-cells that expressed CD10, CD19, CD20, and CD38; 2) typical marginal zone B-cell differentiation; marginal zone B-cells were positive for CD20, CD43, BCL2, and MUM-1, but CD10 and BCL6 negative. A small subset was weakly positive for intracytoplasmic IgM and kappa consistent with early plasmacytic differentiation; 3) Plasmacytoid forms, intracytoplasmic globules and crystals strongly expressed intracytoplasmic monotypic IgM and kappa.

1. Introduction

The 2016 World Health Organization (WHO) classification has categories for rare types of low-grade B-cell lymphomas affecting children and young adults that include pediatric-type follicular lymphoma (PTFL), pediatric nodal marginal zone lymphoma (PNMZL), and pediatric extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue [1]. PTFL and PNMZL present as localized lesions and preferentially affect males. Clinically, PTFL and PNMZL have excellent prognoses with rare relapses and disease progression [2–4]. Although conservative management is proposed, no other therapeutic consensus is specified currently. Detailed criteria for diagnosing PTFL and PNMZL and distinguishing them from other related lymphoma entities are well summarized in a recent review article [5]

While follicular lymphoma (FL) is the most common distinct *disease entity* in the Western world, PTFL comprises 1–2% of all pediatric lymphomas, hence rare. PTFL typically presents with cervical lymphadenopathy. Also, involvement of the Waldeyer ring, tonsils, and testis has been reported [2,6]. PTFL demonstrates partial or complete effacement of nodal architecture. PTFL often exhibits large, expansile and irregular follicles with mainly centroblasts. Mitotic activity is high, and frequent apoptotic cells are present. Mantle zones are attenuated or absent. Immunophenotypically, the follicle center B-cells have been shown to express CD20, CD10, and BCL6 with expanded network of fibrillary fibers of follicular dendritic cells with CD21 and CD23 stains. Ki67 staining was moderate to high (50–75%). BCL2 protein expression as well as *BCL2* gene abnormalities were absent in most cases, but the presence of BCL2 protein expression correlated with worse outcome [2]. Clonal gene rearrangements were reported in all cases, but in only two studies [3,7]. The commonest mutated genes in PTFL were IRF8 (50%) [8], MAP2K1 (~40%) [9], and TNFRSF14 (~30–50%) [7,9].

In contrast to adult marginal zone lymphoma, PNMZL, a provisional entity in the WHO classification, has a high male to female ratio of up to 20:1 and commonly involves neck lymph nodes rather than extranodal sites [4,10]. Morphologically, PNMZL shows partial to complete effacement of nodal architecture. Marked proliferation of the marginal zone B-cells results in prominent marginal and interfollicular patterns. Scattered progressively transformed germinal centers with benign mantle zones surrounded by the marginal zone cells with clear cytoplasm is very common [10]. Also, because the marginal zone B-cells colonize (invade) benign follicles, which results in expansion of follicular centers and attenuated mantle zones, it can mimic a follicular lymphoma [10]. The immunophenotypic profile of PNMZL has been shown to be nonspecific with expression for CD20, CD43, BCL2 (42% of cases), and IgD (24% of cases), but negative for CD5, CD10, CD23, and BCL6 [10]. PNMZL could have numerical abnormalities in chromosomes 3 (trisomy 3, 4%) and 18 (trisomy 18, 17%) [11]. PNMZL could also be shown to be clonal by PCR gene rearrangement studies (75–84% of cases) [10,11]. No recurrent mutated gene mutation was identified in

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PNMZL using whole-exome deep sequencing analysis; however, a somatic variant in AMOTL1 was identified in one case of PNMZL [8].

We report the first case of pediatric B-cell lymphoma with three major malignant components: follicular lymphoma, follicular lymphoma with marginal zone B-cell differentiation, and monotypic plasmacytoid population. Herein, we present the distinctive histopathologic, immunophenotypic, cytogenetic, and gene rearrangement findings and our approach towards reaching a final diagnosis. To our knowledge, a case with three malignant components similar to ours has not been previously reported in both PTFL and PNMZL.

2. Case report

A 15-year old boy presented with right-sided groin swelling; a radiographic CT-scan revealed a localized lymph node mass, which was excised. Post-resection PET/CT study showed only post-surgical changes, no fludeoxyglucose (FDG)-avid soft tissue mass or lymphadenopathy, and no residual mass. Subsequent laboratory work-up was normal. After resection and diagnosis, the patient has not received any treatment and is alive and well 13 months later.

Grossly, the resection specimen weighed 40-g and measured 5.5 × 4.5 × 3.5 cm. Sectioning revealed a homogeneous soft-tan cut surface with focal areas of hemorrhage. An aggregate of three lymph nodes, each measuring up to 1 cm, was attached to the mass. Microscopically, the sections of the mass demonstrated three distinct malignant components: follicular lymphoma, marginal zone B-cell differentiation, and intracytoplasmic monotypic IgM kappa plasmacytic differentiation.

2.1. Follicular lymphoma

Throughout the node, innumerable follicles (~45%) were present. However, in a focal area, there was a striking back-to-back pattern of 11 follicles with absent to very thin and incomplete IgD-positive benign mantle zones that partially encircled the follicles with partial fusion (Fig. 1A, within yellow outline). Hence, morphology of a typical follicular lymphoma was present. This back-to-back arrangement of a few follicles was additionally seen in a couple of other remaining nodal areas. Moreover, throughout the node, there were small, medium, and large follicles completely or partially surrounded by very thin rims of IgD-positive benign mantle zones. Overall, the IgD-positive benign mantle cells comprised approximately 5% of cells. Cytologically, the follicular center cells were essentially of medium and large size with open chromatin structure, absent to indistinct to very small nucleoli and scanty cytoplasm (blastoid) (Fig. 1B). These cells did not have distinct membrane-bound nucleoli like that seen in small and large centroblasts. These cells were positive for CD20 (Fig. 1C), CD10 (Fig. 2A), and BCL6, but essentially negative for BCL2 since only four germinal center cells were BCL2-positive. However, CD3-positive T-cells within germinal centers and in the interfollicular areas were strongly BCL2-positive. Overall, the CD3-positive T-cells comprised 20% of the cells. The follicular lymphoma cells were negative for CD43 and IgM, and no light chain restriction was identified in the follicular center cells by immunohistochemistry. However, admixed subset of marginal zone B-cells were weakly positive for cytoplasmic IgM. The plasmacytoid forms, on the other hand, were strongly IgM-positive and also showed monotypic intracytoplasmic kappa; these plasmacytoid forms comprised approximately 5% of the cells in the follicles. The proliferation marker Ki67 (Fig. 2B) was high within germinal centers. The CD21 immunostain was positive in only the follicular dendritic cells. Focally (~2%), the periphery of the node was benign.

2.2. Marginal zone B-cell differentiation component

The interfollicular areas were markedly expanded by a massive proliferation of innumerable, poorly-defined, closely-packed, small clusters of medium-sized marginal zone B-cells (~25%). These cells have pale to clear staining cytoplasm that produced a prominent interfollicular pattern (Fig. 3A). These marginal zone B-cells were two to three times the size of small benign lymphocytes, with an open chromatin, indistinct nucleoli, and clear cytoplasm (Fig. 3B). Importantly, many marginal zone B-cells also demonstrated plasmacytic differentiation as evident by the presence of abundant eosinophilic cytoplasm that imparted a purple-pinkish hue to this population at low magnification (Fig. 1A within green squares, Fig. 3A). These marginal zone B-cells were positive for CD20, MUM-1 (Fig. 3C), CD43, and BCL2. The marginal zone B-cells were weakly positive for intracytoplasmic IgM and kappa in a small subset of cells, which suggested initiation of early plasmacytic differentiation. The marginal zone B-cells were negative for CD10 (Fig. 2A) and BCL6; hence, the immunophenotype of typical marginal zone B-cells. The proliferative activity of Ki67 stain in the interfollicular areas was low (Fig. 2B).

2.3. Intracytoplasmic monotypic IgM kappa plasmacytoid cells

Present within germinal centers and interfollicular areas as well as beneath the capsule were small and large abnormal-appearing plasma cells and plasmacytoid forms with intracytoplasmic eosinophilic inclusions and globules (Fig. 4A–D), consistent with Russell bodies and Mott cells (Fig. 4B). Also, many extracellular large globular crystals (Fig. 4D) were present in interfollicular areas. These plasmacytoid forms, overall were ~5% of the cells, exhibited monotypic intracytoplasmic kappa light chain (Fig. 4C, D) and were positive for CD138, MUM-1, and IgM, but negative with CD20, IgG, IgD, and IgA.

2.4. Ancillary studies

Flow cytometric analysis revealed a kappa monotypic B-cell population (9% of cells) that expressed surface CD10, CD19, CD20, and CD38. Fluorescence in situ hybridization (FISH) cytogenetic studies showed no clonal chromosomal abnormalities involving *BCL2*, *BCL6*, or *immunoglobulin heavy chain* (*IgH*) genes. No trisomy 3 or trisomy 8 was evident. Moreover, no monoclonality was identified by immunoglobulin heavy chain and kappa light chain gene rearrangement studies by polymerase chain reaction (PCR). No MYD88 mutation was detected by Sanger sequencing.

3. Discussion

Because PTFL and PNMZL are very rare, pathologists have little experience in recognizing them. If pathologists depend upon ancillary studies to establish clonality or malignancy, these can be negative. For example, no BCL2 staining and lack of light chain restriction by immunohistochemistry in the follicular center B-cells is seen in PTFL. Also, the absence of translocations of *BCL2, BCL6, MYC*, and *IRF4* gene rearrangements adds to the diagnostic difficulty, as in the current case. This diagnostic dilemma can be accentuated by the absence of monoclonal immunoglobulin heavy chain by PCR, as in the current case. The absence of clonal B-cell gene rearrangements might be due to somatic hypermutation of the IgH and IgK loci, the probes for which were not able to bind to the DNA; hence the targets could not be amplified, which resulted in the absence of gene rearrangements

The diagnosis and differential diagnosis of PTFL and PNMZL have been discussed in several publications [2–4,10,11], and most recently by Koo and Ohgami [5]. Hence, we will not dwell on these further.

Importantly, in our case, careful histologic review of H&E slides was most useful in making an accurate diagnosis since distinct patterns/pathologic processes were evident at low magnification that are seen in lymphomas and not benign processes: 1) Specifically, a focal area at the periphery of the lymph node, in one section, had “mass effect”, a histologic feature that is common in nodular lymphocyte predominant Hodgkin lymphoma, occasionally seen in low-grade lymphomas, but rare in benign lymph nodes. 2) Within the node, there was complete