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Case study

The utility of IgM, CD21, HGAL and LMO2 in the diagnosis of pediatric follicular lymphoma

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Summary Pediatric follicular lymphoma (pFL) is a rare neoplasm with features differing from follicular lymphoma arising in adults. Here, we describe a rare case of pFL that showed morphologic features partially overlapping with progressive transformation of germinal centers and reactive follicular hyperplasia. As typical of pFL, neoplastic B cells within follicles did not express B-cell leukemia/lymphoma 2 (BCL2). However, this case showed additional distinctive abnormal findings, which contributed to the diagnosis: (1) diffuse and uniform staining of immunoglobulin M (IgM) on cells within and outside of follicles, (2) abnormally dim expression of CD21 on follicular dendritic cells, and (3) expression of human germinal center–associated lymphoma (HGAL) and LIM domain only 2 (LMO2) on B cells in interfollicular and follicular areas. This case demonstrates the utility of these abnormal features, which can be seen in adult- or usual-type follicular lymphoma, in the diagnosis of pFL. Further studies are necessary to evaluate the significance of these findings in other cases of pFL.

1. Introduction

Pediatric follicular lymphoma (pFL) is a rare variant of follicular lymphoma occurring predominantly in children and adolescents [1]. Among the pediatric population, pFL comprise less than 6.5% of childhood lymphomas with an age range between 3 and 18 years, although involvement of older patients has been described [2-6]. pFL tends to show a greater male preponderance with a male/female ratio of 4-11:1. Clinically, it can present in cervical or peripheral lymph nodes, epididymis, testis, Waldeyer ring, gastrointestinal tract, or kidneys [3,7,8]. pFL demonstrates a generally indolent course, shows excellent response rates with excision alone or in combination with systemic chemotherapy, and has a very low-to-almost-no potential for recurrence with localized disease [3,8]. Indeed, many patients present with localized stage I disease despite morphologically high-grade cytologic features. The immunophenotypic and molecular findings in pFL differ from follicular lymphomas in adults; pFL is negative for B-cell leukemia/lymphoma 2 (BCL2) protein expression, lacks the hallmark *BCL2* translocation t(14;18)(q32;q21), and may show morphologic features

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mimicking a benign process. However, pFL remains a neoplastic clonal proliferation, with a B-cell clone typically detected by flow cytometry and/or immunoglobulin (Ig) gene receptor rearrangement studies.

Recent studies have identified human germinal center–associated lymphoma (HGAL) and LIM domain only 2 (LMO2) as specific markers of germinal center B cells; these proteins have additionally been shown to be expressed in adult- or usual-type follicular lymphomas (uFLs) in adults and can be useful in differentiating these lymphomas from other B-cell neoplasms [9]. In addition, abnormal staining patterns of IgM (IgM) and CD21 have been shown to be of utility in diagnosing follicular lymphoma in adults [10,11]. However, these features have not been carefully evaluated in pFLs.

Here, we describe a rare case of pFL, which showed some morphologic features overlapping with reactive follicular hyperplasia and progressive transformation of germinal centers (PTGC); however, abnormal immunophenotypic features allowed for an accurate diagnosis, notably: (1) a diffuse, uniform staining pattern of IgM within follicles and among interfollicular B cells, (2) abnormal follicular dendritic cells with dim CD21 expression, and (3) follicular and interfollicular B cells with HGAL and LMO2 expression.

2. Materials and methods

2.1. Case report

The patient was a 12-year-old previously healthy boy who presented with a firm, tender left parotid mass that had been gradually increasing in size for approximately 1 and a half months. A computer tomographic scan was performed, which demonstrated a 3.5 × 3.0-cm mass within the left parotid gland. No other masses, abnormalities, or lymphadenopathy were seen elsewhere. He was initially treated with antibiotics without resolution, which prompted subsequent fine needle aspirate biopsies of the mass and finally an excisional biopsy.

2.1.1. Clinical data, morphology, flow cytometry, and immunohistochemistry

Clinical data were reviewed in the patient's electronic medical record charts. Cytospin slides were made using fine needle aspirate material and visualized with a Wright-Giemsa stain. Hematoxylin and eosin slides of the excisional biopsy were prepared with standard processing and embedding protocols and cut at 4 μmol/L. Immunohistochemical staining was performed as previously described [9]. Flow cytometric immunophenotyping was performed on a FACSCanto II (BD Biosciences, San Jose, CA).

2.1.2. Molecular and cytogenetic studies

Ig heavy chain (*IGH*) and *Ig κ chain*, *TCR γ*, and *TCR β* gene rearrangements were performed using BIOMED-2 primers followed by differential fluorescence detection [12]. Fluorescence in situ hybridization studies for *MYC*, *BCL2*, and *BCL6* translocations were performed as previously described [13].

3. Results

3.1. Pathologic findings

3.1.1. Fine needle aspirate biopsies

Two concurrent fine needle aspirate biopsies were initially performed, which showed similar features. Wright-Giemsa–stained slides showed 2 populations: (1) scattered smaller atypical mononuclear cells with cleaved nuclei and condensed nuclear chromatin without distinct nucleoli, and (2) larger atypical mononuclear cells with oval-to-irregular nuclear membranes, with variably prominent nucleoli and finer nuclear chromatin (Fig. 1A). Flow cytometry performed on both fine needle aspiration specimens showed an abnormal κ monotypic CD19-positive B-cell population with a subset showing dim-to-negative CD10 expression; no co-expression of CD5 was observed (Fig. 1B-D). Together, these findings were best described as an atypical B-cell proliferation in both cases with the suggestion to perform an excisional biopsy of the mass for definitive diagnosis.

3.1.2. Excisional biopsy

Excisional biopsy of the left parotid mass showed an enlarged lymph node with surrounding unremarkable parotid glandular tissue. Morphologically, the normal lymph node architecture was effaced by a proliferation of abnormal follicles with large, expansile centers (Fig. 2A-C). A subset of these follicles appeared to merge into one another, whereas others showed some features of reactive follicular hyperplasia, with rare tingible body macrophages and numerous mitotic figures. Other follicles had abnormal mantle zones, some with an appearance of involution suggestive of atypical PTGC. Most follicles showed increased centroblastic cells with scattered smaller centrocytic forms. Interfollicular areas were expanded as well and showed scattered atypical small lymphoid cells with cleaved nuclei scattered among histiocytes and plasma cells (Fig. 2).

Immunohistochemical staining was performed to further evaluate the lymph node. CD20 highlighted the large and small atypical cells within the follicles and an abnormally increased number within the interfollicular areas. Scattered CD3-positive T cells were present predominantly in interfollicular regions, whereas a BCL2 stain was negative on the B cells both within follicles and in interfollicular areas (data not shown).

Interestingly, immunohistochemical stains for HGAL (Fig. 2D) and LMO2 (Fig. 2E) stains were positive on the neoplastic B cells within the follicles and retained strong staining on neoplastic B cells in the interfollicular regions (Fig. 2D-E); CD10 was predominantly negative on follicular B cells and absent on the interfollicular expansion