Pediatric-Type Indolent B-Cell Lymphomas With Overlapping Clinical, Pathologic, and Genetic Features

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Abstract: Pediatric-type follicular lymphoma (PTFL) and pediatric nodal marginal zone lymphoma (PNMZL) are rare pediatric-type indolent B-cell lymphomas (PedIBCL) that differ clinicopathologically from their adult counterparts. Accurate diagnosis is important to avoid overtreatment but is often challenging. The mutational landscape of PTFL is known and may aid diagnosis, but the genetic features of PNMZL are not well understood. We analyzed 21 cases of PedIBCL according to their clinicopathologic findings and classified them into PTFL (n = 11), PNMZL (n = 2), and “mixed type” tumors (n = 8) showing ambiguous histology. We also analyzed 2 cases of adult B-cell lymphomas showing features of PedIBCL. Targeted sequencing of 121 lymphoma-related genes was performed. The median age of PedIBCL patients was 16 years (range: 3 to 47), and all but 1 PTFL patient were male. All patients presented with limited-stage disease, and only 1 relapsed. There were no significant differences in clinical features among the 3 PedIBCL groups. The most frequently mutated genes were MAP2K1, TNFRSF14, KMT2C, IRF8, and NOTCH2. The genetic features of all groups were similar to the established mutational landscape of PTFL. The 2 adult B-cell lymphomas cases also had MAP2KI, TNFRSF14, and IRF8 mutations, but the clinical features were not typical of PedIBCL. In summary, this study demonstrated that PTFL and PNMZL are similar diseases with overlapping clinical, pathologic, and genetic features; mixed type tumors can also occur. Atypical adult cases with similar histologic features were also observed. Therefore, the disease spectrum of PedIBCL may be much broader than is currently believed.

Key Words: pediatric-type follicular lymphoma, pediatric nodal marginal zone lymphoma, pediatric-type indolent B-cell lymphoma, targeted gene sequencing (Am J Surg Pathol 2022;46:1397–1406)
folicular growth pattern because of progressive transformation of germinal center (PTGC)-like changes and hyperplasia of the reactive follicles.

Meanwhile, PTFL and PNMZL share many clinical characteristics; they both predominantly affect young males, present as a limited-stage nodal disease in the head and neck region, and show an indolent clinical course with remission after complete resection in most cases. Because of their indolent behavior and favorable outcomes with minimal treatment, accurate diagnosis is important. However, diagnosis is often challenging because their histology can mimic reactive lymphoid hyperplasia and other B-cell lymphomas.

The mutational landscape of PTFL is well known and can aid diagnosis. PTFL lacks the characteristic BCL2 gene rearrangement detected in more than 80% of its adult counterpart, and recurrent mutations in TNFRSF14, MAP2K1, and IRF8 genes have been reported. In contrast, little is known about the genetic features of PNMZL. Cyttogenetic abnormalities, most commonly trisomy 18 and trisomy 3, have been reported, but recurrent genetic alterations were not detected in another series.

The aim of this study was to investigate the clinicopathologic and genetic characteristics of the two rare pediatric-type indolent B-cell lymphomas (PedIBCL), PTFL, and PNMZL, and their diagnostic implications. We performed targeted next-generation sequencing (NGS) using a customized panel of 121 genes involved in the pathogenesis of hematolymphoid neoplasms, and demonstrated that there may be clinical, pathologic, and genetic overlap between the 2 diseases.

**MATERIALS AND METHODS**

**Patients and Samples**

Twenty-two cases diagnosed as PedIBCL, 2 diagnosed as low-grade B-cell lymphoma (LGBCL) with histologic or genetic features of PedIBCL, and 3 diagnosed as atypical lymphoid hyperplasia with PedIBCL included in the differential diagnosis were identified at Seoul National University Hospital (SNUH) and Seoul National University Bundang Hospital (SNUBH) between 2013 and 2021 (Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/PAS/B365). ABCL01 was included in the differential diagnosis including PedIBCL and initially diagnosed as LGBCL with differential diagnosis including PedIBCL were analyzed separately as adult B-cell lymphoma (aBCL), not otherwise specified (NOS) category. Clinical information, including stage, treatment history, and survival, was collected retrospectively from medical records. The study was approved by the Institutional Review Board of SNUH (H-2011-136-1174). Informed consent was waived.

**IHC and B-Cell Clonality Test**

IHC was performed using antibodies against CD3 (clone 2GV6; Ventana Medical Systems, Tucson, AZ), CD20 (clone L26; DAKO, Carpinetia, CA), BCL2 (clone 124; DAKO), BCL6 (clone LN22; Novocastra, Newcastle, UK), CD10 (clone 56C6; Novocastra), MUM1 (clone Ma959; Novocastra), MYC (clone EP121; Cell Marque, Rocklin, CA), Ki-67 (MIB-1; Ventana Medical Systems), PD-1 (clone MRQ-22; Cell Marque), IgD (clone DRN1C; Novocastra), and FOXP1 (clone SP133; Cell Marque) on representative whole FFPE tissue sections. Epstein-Barr virus in situ hybridization was performed using the Bond Ready-to-Use ISH EBER probe (Leica Biosystems, Newcastle, UK) or the INFORM EBER probe (Ventana Medical Systems). Immunostaining was performed using Ventana Benchmark XT (Ventana Medical Systems) or Bond-Max autostainer (Leica Microsystems, Melbourne, Australia) according to the manufacturer’s protocol.

B-cell monoclonality was detected using the IdentiClone IGH Gene Clonality Assay (Invivoscribe Technologies Inc., San Diego, CA).

**Targeted NGS**

Targeted NGS was performed for cases with available FFPE tissue samples using a customized panel of 121 lymphoma-related genes (SNUH FIRST-Lymphoma Panel v1.1; Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/PAS/B366). ABCCL01 had previous sequencing data, obtained from SNUH FIRST-Lymphoma Panel v1.0.

Genomic DNA was extracted from FFPE tissues using the Maxwell CSC DNA FFPE Kit or Maxwell 16 FFPE Tissue LEV DNA Purification Kit (Promega, Madison, WI). Libraries were developed using the SureSelect XT-HS Target Enrichment System (Agilent Technologies, Santa Clara, CA). Paired-end sequencing was performed using the NextSeq 550Dx platform (llumina Inc., San Diego, CA). Sequenced reads were aligned to the reference human genome (GRCh37/hg19) using Burrows-Wheeler Aligner (BWA v0.7.17) and GATK Best Practice (v4.0.2.1). Single-nucleotide variants (SNVs) and small insertions and deletions (indels) were detected by using an in-house developed pipeline, SNVer (v0.5.3) and LoFreq (v2.1.2). Translocations were...
detected using Delly and Mantana, and copy number alterations were called using CNVKit. Mutations were annotated using Snpeff (v4.3).

Mutation Calling and Data Analysis
To identify and remove germline variants and recurrent sequencing artifacts, variants included in an in-house Panel of Normals were excluded. Variants with population frequency over 0.1% on the Genome Aggregation Consortium (gnomAD) East Asian database, Korean Variant Archive (KOVA), or Korean Reference Genome Database (KRGDB) were also filtered out. Mutations with variant allele frequency <2% and fewer than 10 altered reads were called if the same mutation was previously reported in association with hematolymphoid malignancies on public databases, including COSMIC and cBioPortal. Variants with variant allele frequency <2% were also called if the mutation was predicted to be pathogenic or had any clinical significance for PedIBCL according to literature review.

Statistical Analysis
Fisher exact test was performed to compare categorical variables. The Kruskal-Wallis test or Mann-Whitney U test was performed to compare continuous variables. All statistical analyses were performed using SPSS (ver. 25.0; IBM Corp., Armonk, NY). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Classification and Pathologic Features
Eight cases initially diagnosed as PTFL and three initially diagnosed as PNMZL were reclassified as PTFL (Tables 1 and 2; Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/PAS/B367). Three of these cases showed focal marginal zone differentiation, whereas the remaining cases did not (Fig. 1). The cases were classified, by consensus, as mixed type if histologic features of both PTFL and PNMZL were observed. These cases showed expansile follicles with effacement of the nodal architecture, marginal zone hyperplasia with occasional PTGC-like features, and diffuse CD20 staining in both follicular and interfollicular areas (Fig. 2). Four cases initially diagnosed as PTFL, 3 initially diagnosed as PNMZL, and 1 initially diagnosed as indeterminate PedIBCL (PTFL vs. PNMZL) were reclassified as mixed type. All cases reclassified as PNMZL had initially been diagnosed as PNMZL (Fig. 3). A total of 21 cases were finally classified as PedIBCL, including 11 PTFL, 8 mixed type, and 2 PNMZL cases (Tables 1 and 2; Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/PAS/B365).

Clinical Characteristics
There were no significant differences in clinical characteristics, including age, sex, tumor location, stage, treatment modality, and relapse, between the PedIBCL groups (Tables 1 and 2; Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/PAS/B367). The

| TABLE 1. Clinical Features of the Patients |
|------------------------------------------|
| Patient ID | Consensus  | Initial Diagnosis | Age (y) | Sex | Location  | Stage | LDH | Treatment | Relapse | PFS (m) | OS (m) |
|------------|------------|-------------------|--------|-----|-----------|-------|-----|-----------|---------|--------|--------|
| PTFL01     | PTFL w/o MZ| PTFL              | 13     | Male| Head and neck LN | 2B    | 197 | Chemotherapy | No      | 62     | 62     |
| PTFL02     | PTFL w/o MZ| PTFL              | 23     | Male| Head and neck LN | 1A    | 141 | Radiotherapy | No      | 14     | 14     |
| PTFL03     | PTFL w/o MZ| PTFL              | 12     | Female| Head and neck LN | 1A    | NA  | Watchful wait | No      | 46     | 46     |
| PTFL04     | PTFL w/o MZ| PTFL              | 25     | Male| Head and neck LN | 1A    | 145 | Watchful wait | No      | 31     | 31     |
| PTFL05     | PTFL w/o MZ| PTFL              | 17     | Male| Head and neck LN | 2A    | 155 | Watchful wait | No      | 38     | 38     |
| PTFL06     | PTFL w/o MZ| PTFL              | 12     | Male| Head and neck LN | 2A    | 184 | Chemotherapy | No      | 48     | 48     |
| PTFL07     | PTFL w/o MZ| PTFL              | 14     | Male| Head and neck LN | 1A    | NA  | Follow-up loss | No      | 1      | 1      |
| PTFL08     | PTFL w/o MZ| PNMZL             | 20     | Male| Head and neck LN | 1A    | 143 | Chemotherapy | No      | 18     | 18     |
| PTFL09     | PTFL w/o MZ| PTFL              | 32     | Male| Inguinal LN     | 1A    | 454 | Radiotherapy | No      | 68     | 68     |
| PTFL10     | PTFL w/o MZ| PNMZL             | 16     | Male| Head and neck LN | 1A    | 178 | Watchful wait | Yes     | 11     | 30     |
| PTFL11     | PTFL w/o MZ| PNMZL             | 22     | Male| Head and neck LN | 2A    | 186 | Watchful wait | No      | 39     | 39     |
| MIXED01    | PTFL       | PTFL              | 20     | Male| Head and neck LN | 1A    | 143 | Radiotherapy | No      | 17     | 17     |
| MIXED02    | Mixed      | PTFL              | 8      | Male| Head and neck LN | 1A    | NA  | Follow-up loss | No      | 2      | 2      |
| MIXED03    | Mixed      | PTFL              | 16     | Male| Head and neck LN | 1A    | 136 | Watchful wait | No      | 1      | 1      |
| MIXED04    | Mixed      | PTFL              | 47     | Male| Head and neck LN | 1A    | 226 | Watchful wait | No      | 2      | 2      |
| MIXED05    | Mixed      | Pediatric PNMZL    | 3      | Male| Tonsil         | 1A    | 250 | Watchful wait | No      | 54     | 54     |
| MIXED06    | Mixed      | PNMZL             | 15     | Male| Head and neck LN, axillary LN | 2A | NA  | Follow-up loss | No      | 1      | 1      |
| MIXED07    | Mixed      | PNMZL             | 24     | Male| Head and neck LN | 1A    | 172 | Watchful wait | No      | 26     | 26     |
| MIXED08    | Mixed      | PedIBCL           | 8      | Male| Head and neck LN | 2A    | 261 | Chemotherapy | No      | 1      | 1      |
| PNMZL01    | PNMZL      | PNMZL             | 15     | Male| Head and neck LN | 1A    | 159 | Chemotherapy | No      | 61     | 61     |
| PNMZL02    | PNMZL      | PNMZL             | 18     | Male| Head and neck LN | 1A    | 127 | Watchful wait | No      | 1      | 1      |
| ABCCL01    | aBCL, NOS  | Other             | 52     | Female| Head and neck LN, axillary LN, BM | 4A | NA  | Chemotherapy | No      | 14     | 14     |
| ABCCL02    | aBCL, NOS  | Other             | 59     | Male| Head and neck LN | 1A    | 147 | Watchful wait | Yes     | 10     | 33     |

BM indicates bone marrow; LDH, lactate dehydrogenase; LN, lymph node; MZ, marginal zone differentiation; NA, not available; NOS, not otherwise specified; OS, overall survival.
median age was 16 years (range: 3 to 47 y), and most patients were diagnosed as adolescents to young adults. All patients, except 1 PTFL case without marginal zone differentiation (PTFL03), were males. Patients mostly presented with a single mass in the head and neck region regardless of group, and only 1 patient complained of B symptoms. All patients presented with limited-stage disease according to the Ann Arbor staging system, with 15 stage 1A, 5 stage 2A, and 1 stage 2B patients. Serum lactate dehydrogenase levels were below 250 IU/L in 14 of 17 patients.

All 21 patients underwent surgical excision of the involved lymph nodes. Five patients (23.8%) received chemotherapy, and 3 (14.3%) received radiotherapy after excision. Ten patients (47.6%) did not receive any additional therapy after surgery (“watchful waiting”). Only 1 case of PTFL with marginal zone differentiation (PTFL10) relapsed 11 months after complete excision and watchful waiting. The patient remained relapse-free for additional 19 months after re-excision of the involved node.

Mutational Landscape

Targeted NGS was performed in 20 of 21 PedIBCL cases, excluding 1 PTFL without marginal zone differentiation who had no remaining material for NGS study. We detected a total of 52 SNVs or indels in 22 genes, and 4 copy number alterations in 4 genes (Fig. 4). The top 5 most frequently mutated genes were MAP2K1 (40%, 8/20 cases), TNFRSF14 (35%, 7/20 cases, including 1 with multiple mutations), KMT2C (25%, 5/20 cases, including 1 with multiple mutations), IRF8 (15%, 3/20 cases, including 2 with multiple mutations), and NOTCH2 (15%, 3/20 cases, including 1 with multiple mutations). There was no significant difference in the incidence of mutations of these 5 genes among the 3 PedIBCL groups (ie, PTFL, mixed type, and PNMZL) (P > 0.05 for all 5 genes according to the Fisher exact test), or between PTFL and mixed type (P > 0.05 for all 5 genes according to the Fisher exact test) (Table 2). KMT2C was the most frequently mutated gene in PTFL. Four of 10 cases (40%) showed KMT2C mutation, 3 of which were the same KMT2C G908C mutation. Two PTFL cases, 1 with and 1 without marginal zone differentiation,

### TABLE 2. Comparison of Clinical Characteristics and Mutations Between Groups

| PTFL, n (%) | Without MZ, n (%) | With MZ, n (%) | All PTFL, n (%) | Mixed, n (%) | P<sup>*</sup> | P<sup>†</sup> | P<sup>‡</sup> |
|-------------|------------------|---------------|----------------|-------------|-----------|-----------|-----------|
| Number of patients | 8 | 3 | 11 | 8 | 2 | 21 | 2 | — | — | — |
| Median age, y (range) | 15.5 (12-25) | 22 (16-32) | 17 (12-32) | 15.5 (3-47) | 16.5 (15-18) | 16 (3-47) | 55.5 (52-59) | 0.766 | 0.589 | 0.492 |
| Sex (M:F) | 7:1 | 3:0 | 10:1 | 8:0 | 2:0 | 20:1 | 1:1 | 1.000 | 1.000 | 1.000 |
| Location | | | | | | | | 0.738 | 0.429 | 0.678 |
| Head and neck LN | 8 (100) | 2 (66.7) | 10 (90.9) | 7 (87.5) | 2 (100) | 19 (90.5) | 2 (100) | 1.000 | 0.139 | 0.285 |
| Tonsil | 0 | 0 | 0 | 1 (12.5) | 0 | 1 (4.8) | 0 | | | |
| Inguinal LN | 0 | 1 (33.3) | 1 (9.1) | | 0 | 1 (4.8) | 0 | | | |
| Stage at presentation | | | | | | | | 0.109 | 0.058 | 0.092 |
| Limited-stage | 8 (100) | 3 (100) | 11 (100) | 8 (100) | 2 (100) | 21 (100) | 1 (50.0) | | | |
| Advanced stage | 0 | 0 | 0 | 0 | 0 | 0 | 1 (50.0) | | | |
| LDH, IU/L (<250) | 6 (100) | 2 (66.7) | 8 (88.9) | 4 (66.7) | 2 (100) | 14 (82.4) | 2 (100) | 0.682 | 0.471 | 0.525 |
| ≥250 | 0 | 1 (33.3) | 1 (11.1) | 2 (33.3) | 0 | 3 (17.6) | 0 | 1.000 | 0.853 | 1.000 |
| Treatment | | | | | | | | 0.05 for all 5 genes according to the Fisher exact test. |
| Watchful waiting | 3 (37.5) | 2 (66.7) | 5 (45.5) | 4 (50.0) | 1 (50.0) | 10 (47.6) | 1 (50.0) | 1.000 | 0.853 | 1.000 |
| Chemotherapy | 3 (37.5) | 0 | 3 (27.3) | 1 (12.5) | 1 (50.0) | 5 (23.8) | 1 (50.0) | | | |
| Radiotherapy | 1 (12.5) | 1 (33.3) | 2 (18.2) | 1 (12.5) | 0 | 3 (14.3) | 0 | | | |
| Unknown | 1 (12.5) | 0 | 1 (9.1) | 2 (25.0) | 0 | 3 (14.3) | 0 | | | |
| Relapse | 0 | 1 (33.3) | 1 (9.1) | 0 | 0 | 1 (4.8) | 1 (50.0) | 1.000 | 0.238 | 1.000 |
| Median PFS, m (range) | 34.5 (1-62) | 39 (11-68) | 38 (1-68) | 2 (1-54) | 31 (1-61) | 18 (1-68) | 12 (10-14) | | | |
| Median OS, m (range) | 34.5 (1-62) | 39 (30-68) | 38 (1-68) | 2 (1-54) | 31 (1-61) | 26 (1-68) | 23.5 (14-33) | | | |

*P-value for comparison among PTFL, mixed type, and PNMZL.†P-value for comparison between PTFL and mixed type.‡Including 1 case (MIXED06) with main lesion in the head and neck LN and additional involvement of axillary LN.§Including 1 case (ABCL01) with main lesion in the head and neck LN and additional involvement of axillary LN and bone marrow.®Including 1 case (MIXED06) with main lesion in the head and neck LN and additional involvement of axillary LN.†Including 1 case (ABCL01) with main lesion in the head and neck LN and additional involvement of axillary LN and bone marrow.**Including 1 case (MIXED06) with main lesion in the head and neck LN and additional involvement of axillary LN.††Including 1 case (ABCL01) with main lesion in the head and neck LN and additional involvement of axillary LN and bone marrow.®Including 1 case (MIXED06) with main lesion in the head and neck LN and additional involvement of axillary LN.††Including 1 case (ABCL01) with main lesion in the head and neck LN and additional involvement of axillary LN and bone marrow.**Including 1 case (MIXED06) with main lesion in the head and neck LN and additional involvement of axillary LN.††Including 1 case (ABCL01) with main lesion in the head and neck LN and additional involvement of axillary LN and bone marrow.
shared the same MAP2K1 Q56P mutation. One PTFL case without marginal zone differentiation showed TNFRSF14 missense mutation. Two cases with marginal zone differentiation showed TNFRSF14 mutations, one of which was a start loss mutation; the other was a splicing mutation. Only 1 case of PTFL (with marginal zone differentiation) showed an IRF8 mutation, which was a missense mutation (Y23H).

The most frequently mutated gene in the mixed type was MAP2K1. Five of 8 cases (62.5%) had MAP2K1 mutations, all of which were missense mutations. Three mixed type cases had
TNFRSF14 mutations. All 3 cases with TNFRSF14 mutation were originally diagnosed as PTFL. In addition, 2 mixed type cases had multiple missense mutations in the IRF8 gene (K66R and L82V in MIXED07, and Y23H and F36L in MIXED08). None of the mixed type cases had KMT2C mutations.

No mutations were shared between the 2 cases of PNMZL. One case (PNMZL01) showed missense mutations in MAP2K1 (F53I) and KMT2C (G908C) genes, an in-frame deletion mutation of the EP300 gene, and 1 copy loss of the ATM, BIRC3, and CHEK1 genes. The other case (PNMZL02) had a TNFRSF14 nonsense mutation (Q180*) and CREBBP frameshift mutation.

Adult B-Cell Lymphoma, Not Otherwise Specified With Genetic Features of Pediatric-type Indolent B-Cell Lymphomas

The 2 adult cases, separately categorized as aBCL, NOS (ABCL01 and ABCL02), were histologically unusual, with some features of PedIBCL (Fig. 5). ABCL01 showed pure follicular proliferation with a “node within a node” pattern. Neoplastic follicles were composed of intermediate-sized blastoid cells and were negative for BCL2. B-cell monoclonality was detected on IGH gene rearrangement study, and it was initially diagnosed as “LGBCL, type undetermined, with differential diagnoses of PTFL and BCL2-negative adult-type follicular lymphoma.” The clinical features of ABCL01 were not typical for PTFL in that the patient was a 52-year-old female with stage 4 disease involving cervical and axillary lymph nodes and bone marrow. However, targeted NGS performed for diagnostic purposes revealed the typical PedIBCL mutational pattern (Fig. 4). ABCL01 was therefore diagnosed as “LGBCL, type undetermined with genetic features of PTFL.”

In contrast, ABCL02 was a 59-year-old male with a single cervical mass. Histologic examination showed
mixed follicular and interfollicular hyperplasia with scattered PTGC-like changes. B-cell monoclonality was also detected on IGH gene rearrangement study, and the patient was diagnosed as “LGBCL, most likely NMZL with features of PNMZL.” However, the patient relapsed to stage 3 disease 10 months after excision of the cervical lymph node, which was atypical for PedIBCL (Tables 1 and 2; Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/PAS/B367). Targeted NGS was performed in ABCL02, and it also exhibited the typical PedIBCL mutational pattern (Fig. 4).

The 2 aBCL, NOS cases shared the IRF8 K66R mutation and had missense mutations in the same codon (K57) of the MAP2K1 gene. They also had TNFRSF14 mutations, with ABCL01 showing a start loss mutation and ABCL02 showing a missense mutation (C42Y).

**DISCUSSION**

The 2 conventional PedIBCLs (ie, PTFL and PNMZL), are known to share many clinical characteristics, which was also observed in this study. They also have some histologic similarities, in that PTFL may have marginal zone differentiation at the periphery of neoplastic follicles, while PNMZL may show both interfollicular and follicular proliferation. However, the mixed or gray-zone features of PTFL and PNMZL remain unaddressed. In this study, we performed clinicopathologic analysis of 21 PedIBCL cases, including PTFL and PNMZL. By consensus, the cases were reclassified into 3 groups (PTFL, mixed type, and PNMZL) based on histologic findings. PTFL was subdivided into cases with focal marginal zone differentiation and cases with a hyperplastic marginal zone. Half of these cases were originally diagnosed as PTFL (4/8 cases), while 37.5% (3/8 cases) were diagnosed as PNMZL. Three of 11 cases (27.3%) reclassified as PTFL were initially diagnosed as PNMZL. These findings suggest histologic overlap between the 2 diseases and highlight the difficulties in diagnosing these histologically ambiguous cases.

The mutational landscape of PTFL has been well described. Unlike its adult counterpart, it lacks BCL2 gene rearrangement, and mutations in epigenetic modifier genes including KMT2D, CREBBP, and EP300 are less common. Mutations in TNFRSF14, MAP2K1, and IRF8 are also more frequently detected in PTFL. To determine the genetic features helpful for differentiating PTFL and
PNMZL, we performed targeted NGS of 121 lymphoma-related genes. However, the mutational profiles of the three PedIBCL categories were all similar to the previously known mutational profile of PTFL, and no significant differences were found among the categories. PTFL, mixed type, and PNMZL all had recurrent mutations in MAP2K1 (2/10, 5/8, and 1/2 cases, respectively) and TNFRSF14 (3/10, 3/8, and 1/2 cases, respectively) genes. Mutations in IRF8, including the known PTFL-specific alteration K66R, in 1 mixed type case, were also detected in a PTFL case and another mixed type case (1/10 and 2/8 cases, respectively). Although there was a lack of KMT2C mutations in mixed type cases, half of the PTFL and PNMZL cases had KMT2C mutations and shared the same KMT2C G908C mutation. These results suggest overlap in the mutational landscape of PTFL, mixed type, and PNMZL.

Clinically, the mixed type shared features and biological behaviors with PTFL and PNMZL. PTFL, PNMZL, and mixed type were all diagnosed mainly in adolescents and young adult males, and mostly presented as limited-stage disease in the head and neck region. Except for one PTFL case, none of the cases showed progression over the follow-up period of up to 68 months. Because of their indolent course and lack of progression even after the watchful waiting strategy, accurate diagnosis of PedIBCL is important because high-grade lymphomas are more common in the same age group. Recognizing the disease spectra of PTFL and PNMZL, which share clinical, pathologic, and genetic features (as highlighted in this study), will aid appropriate diagnosis and subsequent management of PedIBCL patients.

In this study, we encountered 2 peculiar aBCL cases. These cases were not histologically consistent with any of the conventional B-cell non-Hodgkin lymphomas, and instead had partial PedIBCL features. Consensus review, however, concluded that these cases were not histologically typical of PedIBCL. The clinical course of the two cases was also rather aggressive and atypical of PedIBCL. However, both cases had MAP2K1, TNFRSF14, and

![FIGURE 4. Targeted sequencing for 121 lymphoma-related genes. Mutational patterns and the clinicopathologic characteristics are depicted, and no significant differences in genetic alterations were found according to the consensus diagnosis. CN indicates copy number; Dx, diagnosis; MZ, marginal zone differentiation; NOS, not otherwise specified.](image-url)
IRF8 mutations, which are typical of PedIBCL. In addition, they both had IRF8 K66R mutations, a known hotspot mutation in PTFL. These findings suggest that histologic mimickers of PedIBCL, rarely occurring in adults, may also share its genetic features.

This study raised several questions. Given the shared morphologic and genetic features of PTFL, mixed type, and PNMZL, their diagnostic criteria need to be clarified. Furthermore, whether PTFL and PNMZL are pathogenetically related remains to be clarified. Moreover, marginal zone differentiation in PTFL, even to the level of mixed histology, remains to be investigated. The 3 groups of PedIBCL in this study shared similar clinical, pathologic, and genetic features, and this finding suggests that there may be an overlapping spectrum of disease between PTFL and PNMZL. However, because of small sample size.
sizes, these questions should be further addressed in larger cohorts.

In conclusion, the 2 PedIBCLs were clinically similar conditions with overlapping pathologic and genetic features. There were also some clinically atypical cases that shared the pathologic and genetic features of PedIBCL. This study may expand the currently recognized disease spectrum of PedIBCL.

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