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# Pediatric B-cell Lymphoma, Unclassifiable, With Intermediate Features Between Those of Diffuse Large B-cell Lymphoma and Burkitt Lymphoma: A Report of Two Cases

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B-cell lymphoma, unclassifiable, with intermediate features between those of diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL; intermediate BL/DLBCL) commonly exhibits a morphology similar to that of typical BL and an atypical immunophenotype such as diffuse and moderate-to-strong BCL2 positivity and/or a Ki67 proliferation index <90%. Alternatively, the tumor cells exhibit greater variations in nuclear size and contouring than would be considered acceptable for BL [1, 2]. Intermediate BL/DLBCL is most commonly observed in adults [3-5]. Among pediatric populations, to date, the English literature only includes reports of one case of intermediate BL/DLBCL in a 2-yr-old Korean boy and eight cases in Chinese children [6, 7]. Here, we report two additional cases that represent the first report from a western population.

## Case 1

A 15-yr-old girl with sudden-onset abdominal pain and emesis was found to have a small bowel obstruction and intussusception during a computed tomography (CT) study. An urgent exploratory laparotomy revealed a mass comprising mildly to moderately pleomorphic lymphoid cells that were mostly medium-sized with rare large cells and slightly irregular nuclear contours; these cells primarily contained 2-3 inconspicuous nucleoli or, occasionally, single prominent nucleoli. Mitotic figures were frequent. Focally, tingible body macrophages imparted a "starry sky" appearance. The atypical lymphoid cells were positive for CD20, CD10, BCL-6 (focal, weak), MUM-1, and BCL-2 and negative for terminal deoxynucleotidyl transferase (TdT). The proliferative index, as indicated by Ki-67 staining, was high (>90%; Fig. 1). An Epstein-Barr virus (EBV) study with late membrane protein 1 (LMP1) immunohistochemical stain (IHC) and *in situ* hybridization for EBV-encoded RNAs (EBER), flow cytometric analysis, and karyotyping were not performed. FISH analysis revealed *MYC* rearrangement but no *BCL2* or *BCL6* rearrangement or copy number changes. Three of the 16 resected lymph nodes were also positive for intermediate BL/DLBCL. The patient underwent chemotherapy with cyclophosphamide, vincristine, prednisone, doxorubicin, and methotrexate. She remained in complete remission 11 months after completing chemotherapy.

## Case 2

A 4-yr-old boy with a 2-week history of abdominal distension and

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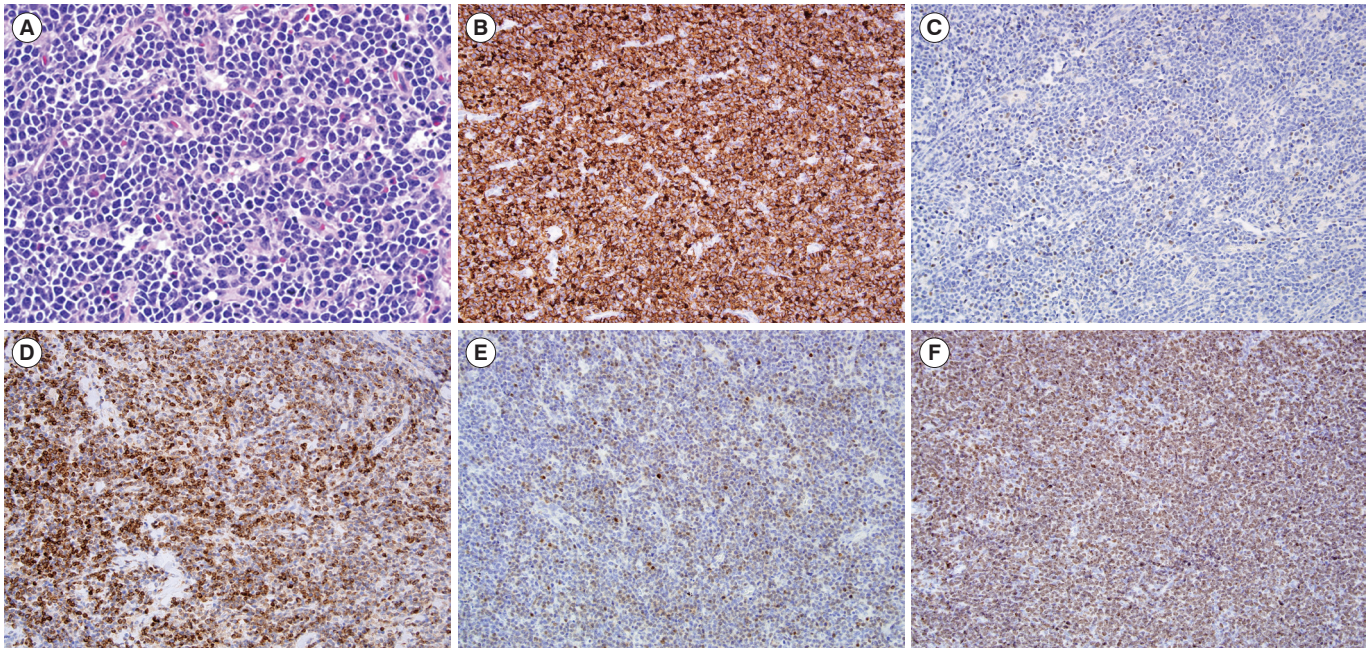


**Fig. 1.** Morphologic (A, Hematoxylin and eosin staining, ×50) and immunophenotypic (B-F, ×20) features of B-cell lymphoma, unclassifiable, with intermediate features between DLBCL and Burkitt lymphoma. (B) CD20, (C) BCL-6, (D) BCL-2, (E) MUM-1, and (F) Ki-67.

**Table 1.** Comparison of the current cases with previously reported intermediate BL/DLBCL cases in English literature

| | Case No. | Sex (N) | Age (yr) | Tissue / Location (Case No.) | Immunophenotype* | FISH for gene rearrangement* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | EBER* | Karyotype | *c-MYC* | *BCL2* | *BCL6* | Follow-up |
| Ahn *et al*. [6] | 1 | M | 2 | Femur neck (1) | CD20, CD10, BCL6, MUM1 (not mentioned), BCL2, Ki-67 (-90%) | 0/1 | Complex | 1/1 | 0/1 | 0/1 | died at 5 months |
| Lu *et al*. [7] | 8 | M (6), F (2) | 4-13 | Abdomen/ intestine (7), gingiva (1) | CD20 (8/8), CD10 (6/8), BCL6 (5/8), MUM1 (5/8), BCL2 (4/8), Ki-67 (60-95%) | 6/6 | ND | 4/8 | 0/8 | 0/8† | NA |
| Current study | 2 | M (1), F (1) | 4, 15 | Intestine (2) | CD20 (2/2), CD10 (2/2), BCL6 (1 strong, 1 weak), MUM1 (1/2), BCL2 (2/2), Ki-67 (90%, 95%) | 1/1 | ND | 2/2 | 0/2 | 0/2 | remission at 11, 12 months |

*positive case number/tested case number; †2 out of 8 cases showed 3 copies of *BCL6*.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; M, male; F, female; ND, not done; NA, not available; EBER, *in situ* hybridization for Epstein-Barr virus-encoded RNAs.

diarrhea was found to have diffuse bowel wall thickening on CT. A transrectal biopsy revealed a diffuse infiltrate of predominantly medium-sized with rare large atypical lymphoid cells; these cells had slightly irregular nuclear contours, vesicular chromatin, and mostly inconspicuous nucleoli. Apoptotic bodies and mitotic figures were frequently observed. The atypical lymphoid cells were positive for CD20, PAX-5, CD10, BCL-6, and BCL-2 and exhibited a high proliferative index, as indicated by Ki-67 staining (> 95%). MUM-1 staining was negative. The EBV study was negative according to LMP1 IHC and EBER *in situ* hybridization. Concurrent flow cytometric analysis revealed a monoclonal B-cell population with CD19, CD20, CD22, CD10, and surface kappa light-chain expression. The monoclonal B cells were negative for CD5, CD23, CD34, and TdT. A cytogenetic analysis (karyotyping) was not performed. FISH analysis with a *MYC* dual-color break apart probe revealed *MYC* rearrangement. There was no evidence of *BCL2/IGH* fusion, *BCL6* rearrangement, or copy number changes in *BCL2* or *BCL6*. The bone marrow and central nervous system were not involved (stage III). This patient received the same chemotherapy regimen as patient 1 and remained in remission for 12 months, as per the last follow-up.

We conducted a systematic review of the pediatric high-grade

mature B-cell lymphoma cases in our archives from 1988 to 2012 and identified 2 cases of intermediate BL/DLBCL. Both cases exhibited histologic morphology compatible with BL but with moderate-to-strong BCL-2 expression. Weak BCL-2 expression might be observed in BL [2]. In our experience, BCL-2 staining has yielded consistently negative or weakly positive (few cells) results in cases of BL. In addition, Case 1 exhibited focal and weak BCL6 expression and moderate-to-strong MUM-1 expression, which would be unusual for a diagnosis of BL [2]. The focal and weak BCL6 staining in Case 2 was not likely caused by poor tissue preservation and/or the stain itself, as the staining of samples from the same tissue block for other nuclear markers (MUM-1 and Ki-67) was successful. To the best of our knowledge, these two cases represent the first report of pediatric intermediate BL/DLBCL in a western population. A comparison of the current cases with previously reported pediatric intermediate BL/DLBCL cases in Asian populations is summarized in Table 1.

The current treatments for pediatric BL, DLBCL, and intermediate BL/DLBCL are similar [8]. However, treatment for patients aged 15-20 yr has been controversial because adolescent DLBCL patients fare better when treated with more aggressive regimens, compared with those who receive a cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-like regimen [9, 10]. Both of our patients were treated with a BL chemotherapeutic regimen. It will be interesting to observe the responses of our patients, particularly the 15-yr-old female patient, during long-term follow-up. With the development of individualized targeted therapies, the recognition of pediatric intermediate BL/DLBCL might become more clinically relevant.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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