Childhood *de novo* CD5+ Diffuse Large B-cell Lymphoma: a Separate Entity?

Amy Coffey[1], Ashleigh Allen[2,3], Matthew B. Thomsen[1,2], Maria Luisa Sulis[4], Vundavalli Murty[1], and Daniela Hoehn[1,2]

[1]Department of Pathology and Cell Biology, Columbia University Medical Center, [2]Department of Pathology and Cell Biology, Divison of Hematopathology, Columbia University Medical Center, [3]Department of Anatomical and Clinical Pathology, Cooper University Medical Center and [4]Department of Pediatrics, Division of Hematology and Oncology, Columbia University Medical Center, New York, NY, USA

Abstract. *De novo* CD5-positive diffuse large B- cell lymphoma (CD5+ DLBCL) is a subtype of DLBCL found predominantly in older individuals. This particular subtype has been associated with a female predominance and a more aggressive clinical course. Conversely, this entity has not been described in the pediatric population. We report a case of a 12 year-old boy who presented with an ileocecal intussusception. Radiologic, morphologic, and immunophenotypic analysis revealed an isolated extranodal mass consistent with a CD5+ DLBCL, germinal center cell phenotype. Fluorescent in situ hybridization analysis was negative for *cMYC, BCL6, BCL2, MLL,* and *IGH/CCND1* rearrangement and showed loss of one copy of MLL in 32% cells. The patient was treated with four cycles of cyclophosphamide, vincristine, prednisolone, methotrexate, and doxorubicin and achieved complete remission. To the best of our knowledge, this is the first detailed report of a *de novo* CD5+ DLBCL occurring in a child.

Introduction

Diffuse large B-cell lymphoma (DLBCL) comprises 40% of adult non-Hodgkin lymphomas in western countries and approximately 15-20% of non-Hodgkin lymphomas in the pediatric population [1,2]. The World Health Organization (WHO) classification scheme currently includes DLBCL under several headings, recognizing specific morphological, immunophenotypic, and molecular variants, which correspond to noteworthy differences in biologic behavior and clinical outcome [1]. While not yet recognized as a separate entity by the WHO, *de novo* CD5-positive DLBCL (CD5+ DLBCL) has been increasingly described by several groups since the initial report in 1995 [3]. These lymphomas comprise approximately (5–10%) of DLBCLs [4], have been shown to arise in older individuals, and show a female predominance. They are associated with a more aggressive disease course [5]; patients often present with increased extranodal and central nervous system (CNS) involvement and more commonly have increased lactate dehydrogenase (LDH) levels. The majority of cases belong to the activated B- cell (ABC) subtype, and associations with specific chromosomal aberrations and molecular features have been reported [5-7].

Conversely, *de novo* CD5+ DLBCL have not been studied in the pediatric population. We report a case of a pediatric *de novo* CD5+ DLBCL, discuss its clinicopathological and fluorescent in situ hybridization (FISH) findings, and provide a brief review of the literature.

Materials and Methods

Case Selection. We searched our departmental archives from July 2004 to July 2014 for cases of high grade B-cell lymphoma (defined by a Ki-67 proliferation index of ≥90%) and pediatric lymphoma simultaneously in order to identify cases with aberrant CD5 expression. The pediatric age range was defined as 0 to 19 years.

Morphologic Evaluation. Hematoxylin and eosin (H&E) stained, formalin-fixed, paraffin-embedded tissue sections were reviewed. Air-dried Wright-Giemsa-stained bone marrow (BM) aspirate smears and H&E stained sections of bouins-fixed, paraffin-embedded bone marrow biopsy cores were assessed.

Address correspondence to Amy Coffey, MD; Department of Pathology and Cell Biology, Columbia University Medical Center, 622 West 168th Street, PH 15 West 1574, New York, NY 10032, USA; phone: 212 305 8533; fax: 212 305 6596; e mail: amc2343@columbia.edu

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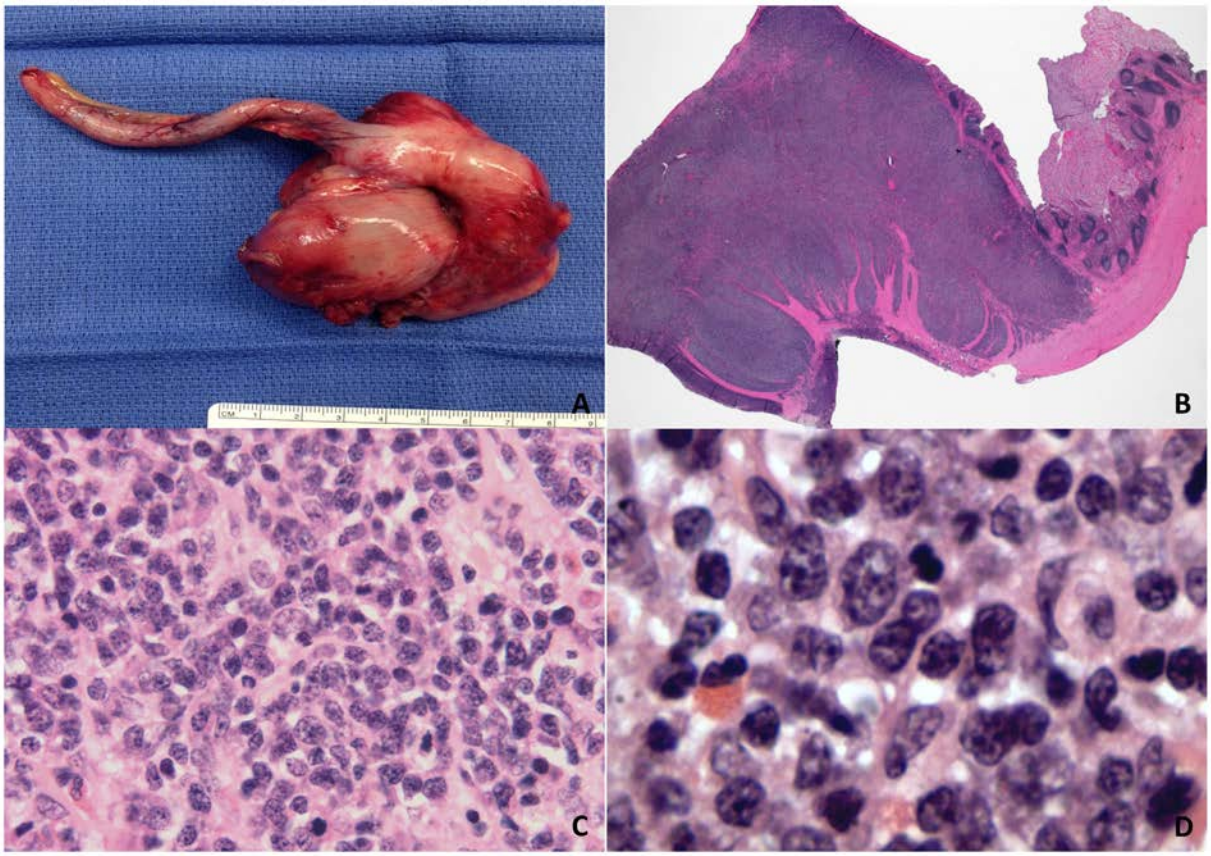

Figure 1. Gross and histologic findings. *Gross and histologic examination showed an ileal mass* ***(A)*** *which consists of a diffuse infiltrate of lymphocytes extending through full-thickness bowel wall* ***(B)****. The neoplastic cells are intermediate to large in size with vesicular to coarse chromatin, variably visible nucleoli and scant to moderate amounts of cytoplasm admixed with frequent mitotic figures (including atypical mitosis) and apoptotic bodies.* ***(C,D)****. B: H&E 20x, C: H&E 500x, D: H&E 1000x.*

Immunophenotypic Evaluation. Immunohistochemical marker analysis was performed using antibodies against CD5, CD10, CD20, CD21, CD23, bcl2, bcl6, TdT, CD56, CD34, CD3 (Leica Biosystems, Nussloch GmbH, Germany), CD43, CD79a, CD44, CD30, CD138, MUM1, Cyclin D1, Ki-67 (Ventana Medical Systems, Inc., Tucson, Arizona, USA), HGAL, FoxP1, SOX11, LMO2 (Cell Marque, Inc., Rocklin, CA, USA), and c-Myc (Abcam plc., Cambridge, England, UK). *In situ* hybridization for Epstein Barr virus encoded RNA (EBER) was also performed (Ventana Medical Systems, Inc., Tucson, Arizona, USA).

Flow cytometric immunophenotyping was performed on cell suspensions using FACScalibur (BD Bioscience, San Jose, CA) according to standard procedures with monoclonal antibodies consisting of CD45, CD19, CD20, FMC7, cytoplasmic CD79a, CD3, CD5, CD23, CD43, CD10, CD11c, CD25, CD103, CD13, CD33, CD117, CD38, CD138, CD56, surface and cytoplasmic kappa and lambda light chains, surface and cytoplasmic IgM, and surface IgD (BD Bioscience, San Jose, CA). For each antibody, negative staining levels were set by comparison with an isotype-matched control. Data analysis was performed using FACS Diva software (BD Bioscience, San Jose, CA).

Cytogenetic Analysis and Fluorescence in Situ Hybridization. Conventional cytogenetic analysis was performed on metaphase cells from BM aspirate cultured for 24 h using standard techniques. Giemsa banded metaphases were analyzed and described according to International System for Human Cytogenetic Nomenclature 2009 [8]. Fluorescence in situ hybridization (FISH) for *cMYC, BCL6, BCL2, MLL,* and *IGH/CCND1* gene rearrangements was performed on interphase nuclei using break apart probes and a dual color dual fusion probe respectively (Abbott Laboratories, Abbott Park, Illinois, USA).

Results

We identified 25 cases of pediatric B cell lymphoma (age range 3-19 years) with a high proliferative index (Ki-67 ≥90%). According to 2008 WHO classification, the cases were classified as 19 Burkitt lymphomas, 4 DLBCL and two monomorphic post-transplant lymphoproliferative disorders (m-PTLD) [1]. Aberrant CD5 expression was present in only one case.

Clinical history. The patient was a 12 year-old boy with no family history of malignancy and a past medical history significant only for pervasive developmental disorder, not otherwise specified. He presented with approximately 6 weeks of diffuse vague abdominal discomfort, which progressed to intermittent episodes of severe pain associated with bright red blood per rectum. Both upper and lower gastrointestinal endoscopies were performed at an outside institution and an ileocecal intussusception with an intraluminal cecal mass was noted. Biopsy of the mass revealed a hyperplastic polyp. The size of the lesion prohibited endoscopic removal and an ileocecal resection was scheduled. A laparoscopic ileocecectomy with primary anastomoses was performed at our institution; no lymphadenopathy or hepatosplenomegaly was noted during intraoperative examination. Post-operative laboratory values demonstrated mild anemia (hemoglobin 10.6 g/dL), a slightly elevated white blood cell count (WBC 10.3 x 10(9)/L), and a serum lactate dehydrogenase (LDH) of 188 U/L (normal range 115-221 U/L).

Gross examination. Gross examination of the specimen showed a tan-red, firm, fungating mass in the ileum measuring 4.5 cm in horizontal dimension, 3.0 cm in longitudinal dimension, and 1.4 cm in vertical dimension, located 0.5 cm from the ileocecal valve and coming to within 0.1 cm of the serosal surface **(Figure 1A)**. The ileum appeared partially intussuscepted into the cecum. No evidence of perforation was seen. The appendix and mesenteric fat were unremarkable.

Morphologic findings. *Ileocecal Mass.* Microscopic examination showed a dense, full-thickness, diffuse infiltrate of lymphocytes extending from the mucosal surface into the submucosa **(Figure 1B)**. The lymphocytes were intermediate to large in size with oval to irregular nuclei, irregular nuclear contours, vesicular to coarse chromatin, variably visible nucleoli, and scant to moderate amounts of cytoplasm **(Figure 1C-D)**. Apoptotic debris and mitotic figures were abundant and areas of necrosis were noted. Adjacent uninvolved small bowel and appendix showed follicular hyperplasia, unremarkable small bowel mucosa, and luminal mucinous exudates. Six small lymph nodes were noted, all negative for involvement by lymphoma (data not shown).

Bone marrow. Review of bilateral core needle biopsy specimens and aspirate smears revealed a cellular marrow with trilineage maturing hematopoiesis.

Immunophenotypic findings. *Ileocecal Mass.* No fresh tissue was available at the time of diagnosis, precluding flow cytometric evaluation. An extensive immunohistochemical marker panel was performed, demonstrating that the neoplastic cells were positive for CD5, CD10 (variable), CD20 **(Figure 2A-C)**, CD43, CD44 (weak), CD79a, bcl6, HGAL, and FOXP1 with weak expression of bcl2 (data not shown). The cells were negative for CD30, CD34, CD56, CD138, MUM1, TdT, LMO2, Cyclin D1 **(Figure 2D)**, and SOX11. Antibodies for CD21 and CD23 did not show any follicular dendritic cell meshwork and in situ hybridization for EBER was negative (data not shown). C-Myc was weakly positive in about 10 to 20% of neoplastic cells and Ki-67 demonstrated a proliferation index of approximately 90% **(Figure 2E,F)**. CD3, CD5, and CD43 highlighted admixed small background T-lymphocytes. The combined morphologic and immunophenotypic findings were diagnostic of a mature B-cell lymphoma, germinal center cell phenotype, with high proliferation index and aberrant CD5 expression.

Bone marrow. Flow cytometric analysis of the bone marrow aspirate sample and immunophenotypic analysis of the core needle biopsy showed no evidence of marrow involvement by lymphoma (data not shown).

Cytogenetic analysis. *Ileocecal mass.* No fresh tumor tissue was available at time of diagnosis which precluded conventional cytogenetic karyotyping. FISH analysis performed on paraffin-embedded tissue sections was negative for *IGH/CCND1* rearrangement and negative for *cMYC, BCL6, BCL2,* and *MLL* rearrangement/amplification respectively. The *MLL* (11q23) break apart probe showed loss of one copy of *MLL* in 31.7% **(Figure 3)**.

Bone marrow. Karyotype analysis on the bone marrow aspirate revealed a normal male karyotype (46,XY) without evidence of clonal chromosomal abnormalities.

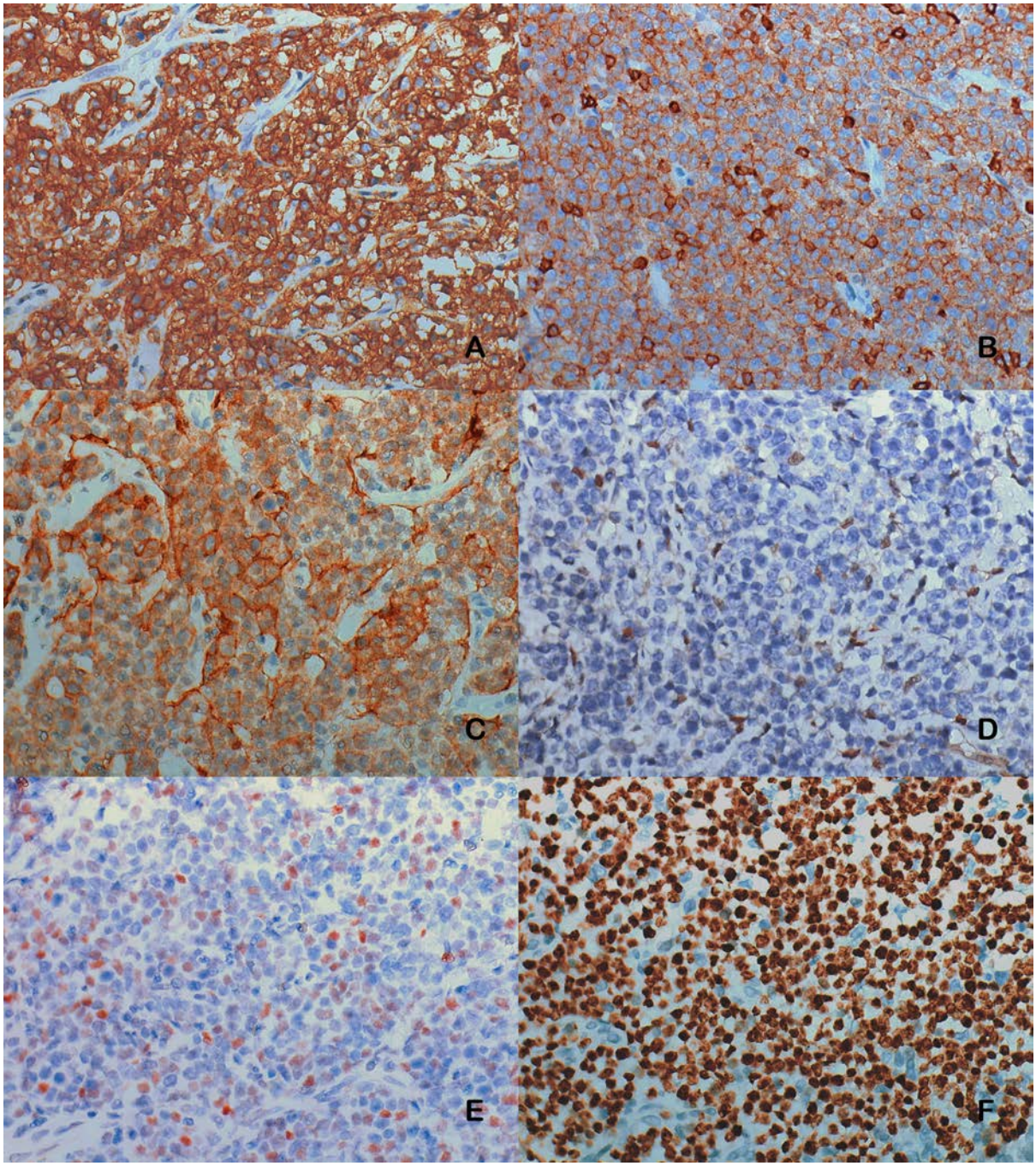

Figure 2. Immunophenotypic findings. *Immunohistochemical studies show the neoplastic cells are positive for CD20* ***(A)****, CD5* ***(B)*** *and CD10* ***(C)****, while negative for Cyclin D1* ***(D)****. An antibody for c-Myc is positive in about 10-20% of the neoplastic cells* ***(E)*** *and Ki-67 highlights a proliferation index of approximately 90%* ***(F)****. A-F: 400x.*

Staging and Therapy. CSF analysis was negative for lymphoma involvement. A whole body positron emission tomography/computed tomography (PET/CT) scan performed post-operatively identified mild FDG activity in the postoperative bed and rare FDG-avid clusters in lymph nodes adjacent to the operative bed, suggestive of reactive inflammatory changes.

The patient was initially classified as having Stage II disease, planned for two cycles of COPAD (cyclophosphamide, vincristine, prednisolone, and doxorubicin), and then later on upstaged, thus receiving four cycles with the addition of methotrexate and intrathecal therapy. The therapy was well tolerated and end of therapy evaluation with PET/CT demonstrated resolution of the previously described

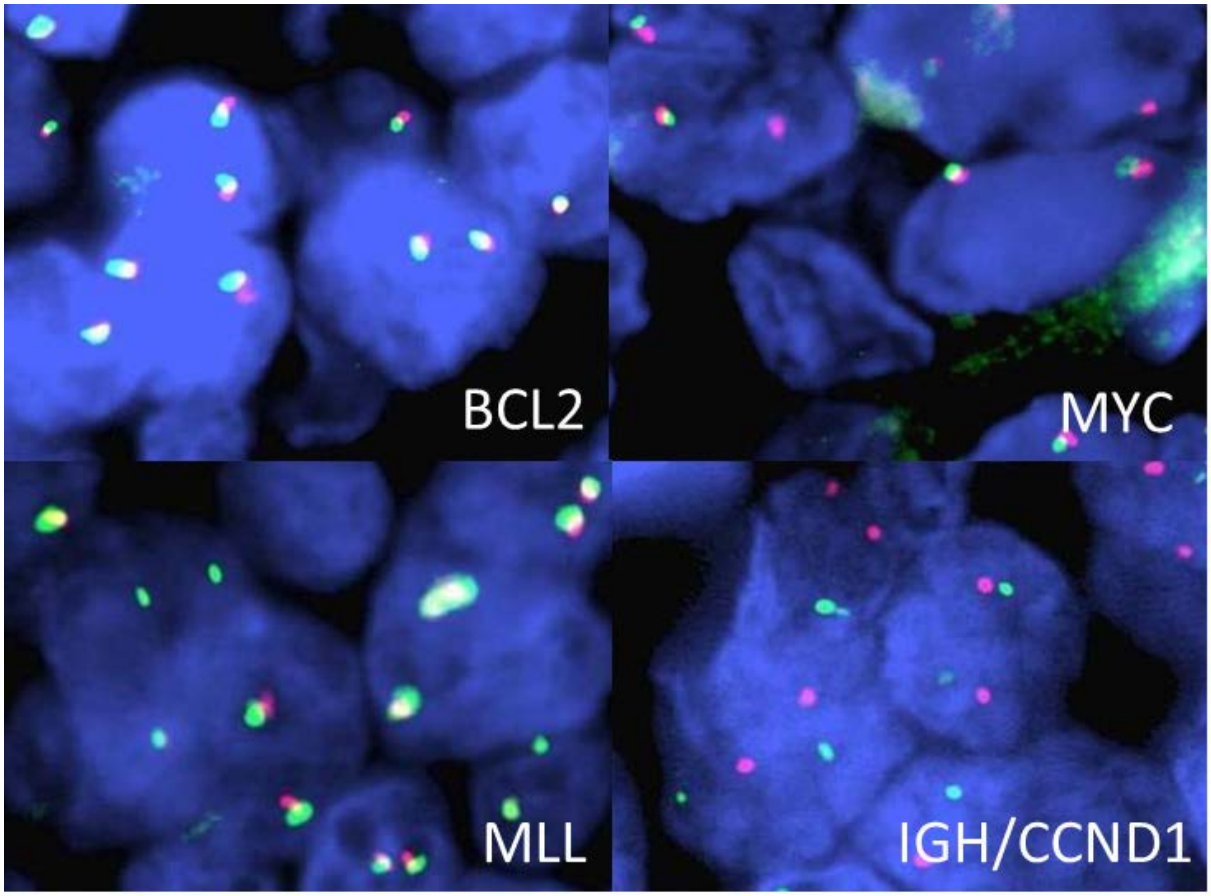

Figure 3. Fluorescent in situ hybridization (FISH) analysis results. *Break apart probes for C-MYC, BCL2, and MLL showed no evidence of rearrangement. The IGH/CCND1 dual color dual fusion probe showed no evidence of translocation. Loss of one copy of the MLL gene was noted in 31.7% of cells.*

FDG avidity in the surgical bed and adjacent lymph nodes. No FDG avid disease was noted elsewhere. A 6 month post end of therapy follow up PET/CT showed no evidence of disease/relapse.

Discussion

Here we describe a case of a mature B-cell lymphoma with high proliferation index and aberrant CD5 expression that presented as an isolated extranodal mass in a 12-year old boy causing an ileocecal intussusception. Initial differential diagnostic considerations encompassed several B-cell lymphoproliferative neoplasms such as Burkitt lymphoma, B-lymphoblastic leukemia/lymphoma, and less likely, mantle cell lymphoma or a rare variant of follicular lymphoma with aberrant CD5 expression [9].

Immunophenotypic findings, particularly the lack of immaturity markers, did not warrant a diagnosis of B-lymphoblastic lymphoma. The patient's age in conjunction with the lack of Cyclin D1 and SOX11 expression by immunohistochemical marker analysis as well as the lack of CCND1 abnormalities by FISH analysis effectively ruled out a diagnosis of mantle cell lymphoma. While a blastoid proliferation/variant of follicular lymphoma could be entertained diagnostically, especially since a subset of these cases can demonstrate CD5 expression and may lack *IGH/BCL2* gene rearrangement, the majority of these cases show a follicular growth pattern, present with multifocal involvement/lymphadenopathy, elevated serum lactate dehydrogenase (LDH) levels, elevated serum β2-microglobulin levels, and are associated with higher International Prognostic Index (IPI) scores [9]. Li *et al.* recently analyzed 88 cases of CD5+ follicular lymphoma and the youngest patient in their cohort was 31 years old [9]. As none of these characteristics were present in our patient, a diagnosis of this rather uncommon B-cell lymphoma appeared less likely.

Table 1. *Summary of published cases of de novo CD5+ DLBCL and patient demographics.*

Author	Year	Number of patients	Median age (years)	Age range (years)	Percent > than 60 years
Yamaguchi et al. [15]	2002	109	66	22-91	75%
Yoshioka et al. [7]	2005	23	67	40-86	NR*
Ennishi et al. [14]	2008	11	68	33-76	84%
Yamaguchi et al. [13]	2008	120	66	22-91	70%
Hyo et al. [16]	2010	19	66	30-91	NR*
Niitsu et al. [17]	2010	102	65	21-85	NR*
Miyazaki et al. [11]	2011	337	67	15-93	NR*

*Not reported

In general age and localization of the tumor were more consistent with a diagnosis of Burkitt lymphoma; however the proliferation index did not approach 100% as would be expected in Burkitt lymphoma. In addition, the observed cytological pleomorphism along with aberrant CD5 expression was rather unusual for a diagnosis of Burkitt lymphoma. While CD5 positive de novo Burkitt lymphoma cases have been described in the literature [10], these cases all presented in elderly patients, in a leukemic phase, with variable lymph node and splenic involvement, typical Burkitt morphology, high proliferative index, and most importantly, *cMYC* rearrangement. None of these clinicopathological parameters were present in our case and FISH analysis was negative for *cMYC* rearrangement or amplification.

For these reasons along with the overall morphologic and phenotypic features as well as the recognition of a specific subtype of DLBCL in adult patients, a diagnosis of CD5+ DLBCL was rendered. To our knowledge, this is the first well-documented case of a *de novo* CD5+ DLBCL occurring in a pediatric patient.

De novo CD5-positive DLBCL has been well-characterized in adults and represents approximately 5-10% of DLBCL in the adult setting. This entity is distinctly different than other CD5+ lymphomas, such as mantle cell lymphoma and Richter's transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma, in regards to combined pathologic and clinical features. Though Richter's transformation presents with elevated LDH, B symptoms, and advanced stage disease, extranodal Richter's transformation is rare. In contrast, while patients with *de novo* CD5+ DLBCL also tend to present with elevated LDH levels, B symptoms, advanced clinical stage, and poor performance status, these patients usually present with extranodal involvement as well as frequent central nervous system (CNS) involvement and do not have a preceding history of a B-cell lymphoproliferative disorder [5,11,12]. The clinico-pathological features of this entity have been confirmed in several studies and review articles in detail [5,11,13-16]. Notably, although the median age in all studies ranged from 65 to 68 years, the youngest patient mentioned in one series was 15 years of age **(Table 1)** [11]. However, further details on this patient were not provided, and it is unknown if the patient had any significant prior clinical history.

Four morphological variants of CD5+ DLBCL have been described, including the common variant (centroblastic/monomorphic variant), the immunoblastic variant, the giant cell rich variant, and the polymorphic variant [13]. Immunophenotypically, adult CD5+ DLBCL fall more often within the ABC- DLBCL subgroup with a typical immunophenotypic profile, characterized as MUM1+, Foxp1+, GCET1-, CD10-, and bcl6- [18]. They also commonly express bcl2 [5]. It is notable that our case rather belonged to the germinal center B-cell (GCB) subtype, with only weak bcl2 expression shown in a subset of cells (data not shown). This finding is in concordance with the fact that the majority of pediatric DLBCL belong to the GCB subtype, with a characteristic immunophenotype of GCET1+, CD10+, bcl6+, MUM1-, and FoxP1- [19,20]. This GCB

predominance is also concordant with the fact that pediatric DLBCL patients have, in general, an overall better prognosis than adults [21]. Other notable characteristics of pediatric DLBCL include moderate to high proliferation rates and increased c-Myc protein expression.

Regarding cytogenetic and molecular features, several differences exist between pediatric and adult DLBCL cases. For example, *BCL2* translocations are rarely seen in children. On the contrary, translocations involving the *cMYC* oncogene are more frequent in pediatric DLBCL compared to adults [22]. In adult CD5+ DLBCL, cytogenetic aberrations have been shown to be similar to those occurring in the ABC- DLBCL setting, including loss of 9p21 ($p16^{INK4a}$ locus), gains of 13q21.1-q34, loss of 1p34.3-p36.21, and chromosome 8 aberrations [5,7].

In our case FISH analysis for *BCL2, BCL6* and *cMYC* did not identify any abnormalities. FISH analysis using the *MLL* (11q23) break-apart probe showed no evidence of rearrangement; however, loss of one copy of *MLL* was seen in 31.7% of cells.

A recent study described a subset of MYC-negative high-grade B-cell lymphomas resembling Burkitt lymphoma that had recurrent aberrations in chromosome 11q by gene expression analysis, suggesting an alternate driving mechanism in some of these neoplasms [23]. However, CD5 expression was not described in any of these cases, and all patients presented more frequently with nodal involvement and high LDH levels. In contrast, our patient did not demonstrate any lymphadenopathy, definitive nodal involvement, or LDH elevation.

Yoshioka *et al.* described different chromosomal aberrations involving chromosome 11 in *de novo* CD5 positive DLBCL [7]. They suggested that the entity of CD5+ DLBCL can be further subdivided into at least two groups that differed in overall survival. They identified a group of patients with 11q13 abnormalities that showed better survival rates and a group of patients with 8p21 abnormalities that was associated with a worse prognosis. In addition, the former group more often presented with localized disease and had less LDH elevation [7].

The findings of the Yoshioka *et al.* study share some similarities to our patient; however, none of the patients in this study were younger than age 40. Therefore, it is not clear if this entity is biologically and prognostically similar to our case.

Based on the lack of data on the prognostic significance of CD5 expression in children, the unusual presentation, the very remote possibility that a PET avid lymph node next to the operative bed might be involved by disease, and the fact that recurrent DLBCL has a very low cure rate, our patient was upstaged and thus received a more aggressive treatment protocol. He tolerated the therapy very well and both, an end of therapy and a 6 months post therapy follow PET/CT scan confirmed complete remission.

Conclusion. In summary, we present the first well-described case of a *de novo* CD5+ DLBCL occurring in a pediatric patient. We report this case to emphasize the unusual presentation and we suggest adding this entity to the extensive list of differential diagnostic considerations in pediatric lymphoid neoplasms. No comments regarding prognosis or therapy can be made on the basis of a single patient; however, it seems possible that the standard therapy used for children carrying a diagnosis of DLBCL may be appropriate.

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