Pediatric blastic plasmacytoid dendritic cell neoplasms are molecularly defined by recurrent *MYB* rearrangements: clinical and molecular insights

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy of plasmacytoid dendritic cells; recent data support skin-based transformation influenced by ultraviolet exposure.[1] Pediatric BPDCN is uncommon (<100 reported cases), and typically presents in children and adolescents without the strong male predominance and clonal myeloid neoplasm association seen in adults.[2-4] Although many children achieve remission with the type of regimens used for acute lymphoblastic leukemia (ALL), relapses and central nervous system (CNS) disease remain clinically relevant and have motivated incorporation of venetoclax, CD123-targeted therapies, and hematopoietic stem cell transplantation in selected cases.[2,5-7] Diagnosis relies on plasmacytoid dendritic cell-associated markers such as TCF4, CD303, and TCL1, with variable expression of lineage-associated antigens alongside CD4, CD56, and CD123.[2,4,8] Genetically, pediatric BPDCN frequently shows copy-number abnormalities involving 13q14 (*RB1*), 9p21.3 (*CDKN2A/B*), 12p13 (*ETV6*, *CDKN1B*), and 7p12 (*IKZF1*).[9] Importantly, *MYB* rearrangements are more prevalent in pediatric BPDCN (~90%) than in adult disease (~44%).[10] However, the full spectrum of *MYB* alterations and cooperating lesions - particularly across skin and bone marrow compartments - remains incompletely defined.

We identified pediatric patients with BPDCN diagnosed between 2000 and 2025 and reviewed their clinical records, pathology materials, and ancillary studies. Cases were confirmed by integrated morphological and immunophenotypic assessment using plasmacytoid dendritic cell-associated markers, when available, with exclusion of alternative lineage-defining neoplasms. Clinical involvement at diagnosis (skin, bone marrow, lymph node, CNS), treatment exposures, and outcomes were abstracted. Available molecular testing included RNA-sequencing, whole-exome/whole-genome sequencing, and/or targeted DNA-based next-generation sequencing performed on involved tissue or bone marrow; structural variants, somatic single nucleotide variants/indels, and copy-number alterations were annotated and summarized (*Online Supplementary Figure S1, Online Supplementary Table S1*). The study was conducted with institutional review board approval in accordance with the Declaration of Helsinki.

The cohort comprised 21 patients (12 males, 9 females) with a median age at diagnosis of 12 years (range, 5-18 years). No patient had a documented prior myeloid neoplasm. At presentation, cutaneous involvement was documented in 16/20 evaluable cases (80%), with bone marrow involvement in 9/16 (56%), lymph node involvement in 8/14 (57%), and CNS involvement in 5/11 (45%). Site-stratified clinical characteristics are summarized in Table 1. Among adequately staged cases, presentations were categorized as skin-only (3/15, 20%), skin plus systemic (bone marrow and/or other extramedullary disease; 8/15, 53%), or systemic-only disease (4/15, 27%). No association was observed between clinical presentation and *MYB* rearrangements. Representative paired skin and bone marrow morphology from case 1 is shown in Figure 1.

MYB-region alterations defined pediatric BPDCN in this cohort and expanded the spectrum of reported events. Eighteen cases underwent RNA-sequencing or RNA fusion panel testing, but only 12 yielded informative results for assessing *MYB* or *MYBL1* rearrangements; 11 of these 12 informative cases harbored *MYB* or *MYBL1* alterations. Detected events included *MYB*::*DCPS* (N=4), *MYB*::*PLEKHO1* (N=2), *MYB*::*ZFAT* (N=1), truncating *MYB* structural variants without a defined 3' partner (N=2), a peri-*MYB HBS1L*::*UGCG* fusion (N=1), and *MYBL1*::*MTFR1* (N=1). In the pediatric literature reviewed in *Online Supplementary Table S2*, peri-*MYB HBS1L*::*UGCG* and *MYBL1*::*MTFR1* were not previously reported. Case 5 also showed a truncating *ETV6* rearrangement predicted to disrupt exon 3 in the context of a concurrent *MYB*::*DCPS* fusion. Breakpoints were heterogeneous; genomic coordinates are provided, when available, in *Online Supplementary Table S1*.

The *MYB* fusions and truncations observed are predicted to preserve the DNA-binding and transactivation domains while lacking the C-terminal negative regulatory domain. Loss of the negative regulatory domain is associated with constitutive *MYB* activity and deregulation of oncogenic targets, including *MYC, BCL2, KIT*, and *ERBB2*.[7,10] Truncated *MYB* alleles uniformly lacked the negative regulatory domain, supporting loss of this domain as a shared oncogenic mechanism across diverse *MYB* structural variants. Functional studies by Booth *et al*. demonstrated that BPDCN-associated *MYB* fusions redirect transcriptional programs away from normal dendritic cell differentiation toward aberrant G2/M cell-cycle regulation and are sufficient to induce a myeloid-dendritic leukemia phenotype *in vivo*.[11] The peri-*MYB HBS1L*::*UGCG* event was located upstream of *MYB* and is most consistent with a *cis*-regulatory alteration affecting *MYB*. After normalization, this case showed *MYB* expression comparable to that in *MYB*-altered cases and higher than in other tumors tested in our laboratory.

Somatic oncogenic variants were identified in a subset of cases, with activating *RAS*-pathway alterations representing the most frequent cooperating events (*NRAS*, N=6 [43%]; *KRAS*, N=2 [14%]) (*Online Supplementary Figure S1*). Additional point mutations involved *RB1* and *KMT2C/KMT2D* (2 cases each; 14%) and single cases of *CDKN1C, IKZF1, NF1,* and *TP53* (7% each). Copy-number alterations were most frequent in *IKZF1, CDKN2A*, and *CDKN2B* (3/7, 43% each), followed by *ETV6* and *JAK1/2* (2/7; 28% each), and *TCF4* and *TP53* (1/7; 14% each). Recurrent chromosomal losses involved 12p (6/7, 86%), 13q (6/7, 86%), 9q (6/7, 86%), 17p (4/7, 57%), and 6q (3/7, 43%). *TP53* disruption was observed in case 5, with concurrent mutation and 17p loss. These patterns are consistent with prior pediatric BPDCN reports and underscore convergence on key pathways regulating cell-cycle control (*RB1; CDKN2A/B*), transcriptional regulation (*IKZF1; ETV6*), and signaling pathways (*RAS*).[9,10]

We observed monoallelic *TCF4* deletion in one case (case 2) (*Online Supplementary Figure S1*). *TCF4* is a lineage-survival oncogene and a reliable diagnostic immunophenotypic marker; experimental downregulation disrupts super-enhancer–associated transcription and induces apoptosis in BPDCN models.[8] Beyond its oncogenic role, *TCF4* is required for plasmacytoid dendritic cell lineage specification, raising the possibility that haploinsufficiency may influence differentiation state or therapeutic vulnerability. Paired-site molecular profiling was available in one patient (case 1). In this patient, the skin lesion harbored *MYB*::*PLEKHO1* and *KRAS* G12C, whereas concurrent bone marrow RNA-sequencing, whole-exome sequencing, and whole-genome sequencing did not detect these alterations. *RAS*-pathway alterations were also detected in the bone marrow in a subset of cases, underscoring the value of multi-compartment profiling when feasible. These findings are consistent with adult studies linking *RAS*-pathway alterations to systemic disease and history of sun-exposure,[12,13] and with pediatric reports identifying *NRAS* and other signaling mutations in skin/lymph node or bone marrow, depending on disease presentation.[5,6]

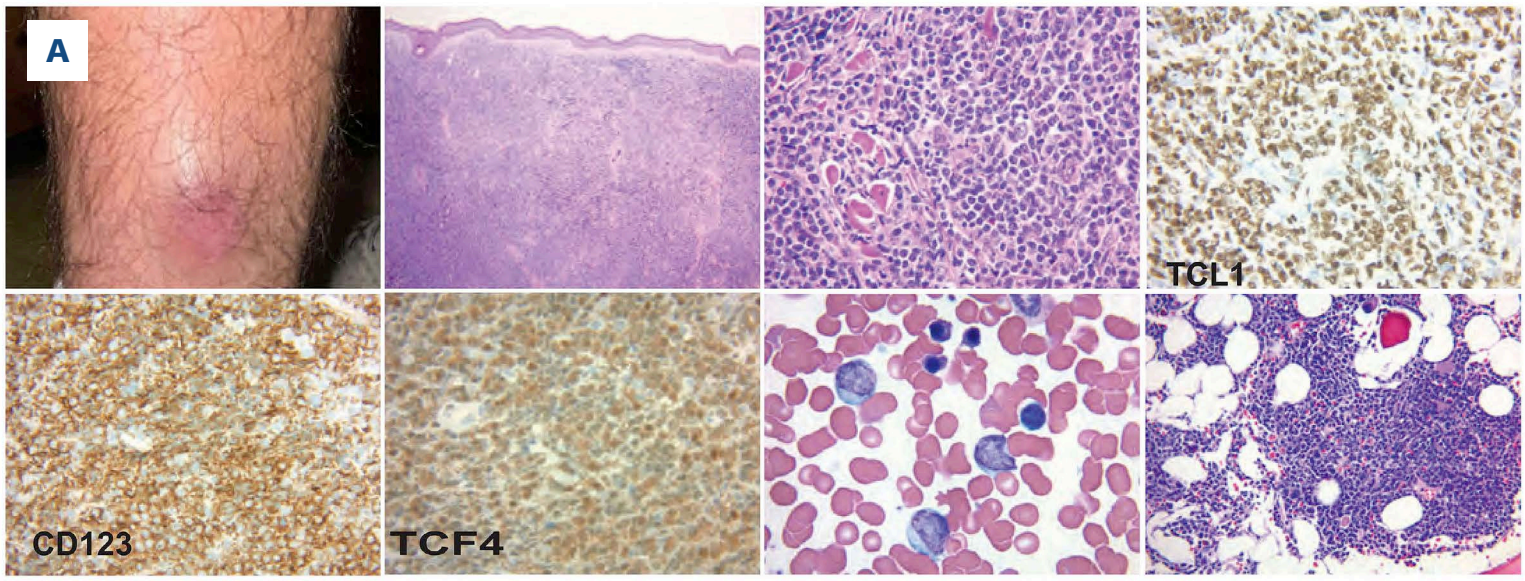
Review of published pediatric BPDCN cases with molecular characterization (≤20 years; N=25) (*Online Supplementary Table S2*) showed predominant skin involvement: reported skin-only disease (N=5, 20%), skin plus systemic (N=15, 60%), and systemic-only disease (N=5, 20%). In contrast to adult cohorts, which are enriched for *TET2, ASXL1, ZRSR2*, and other splicing factor mutations and may show clonal relationships to myeloid neoplasms, pediatric *MYB*-rearranged cases have fewer documented cooperating mutations, with recurrent alterations involving *ETV6, KMT2C/KMT2D, IKZF1, NRAS*, and *CDKN2A*.[3,12,14] Together, these findings support *MYB* rearrangements as dominant initiating lesions in pediatric BPDCN, with subsequent acquisition of cooperating alterations (including *RAS*-pathway lesions) that may influence tissue dissemination and clinical phenotype (Figure 2).

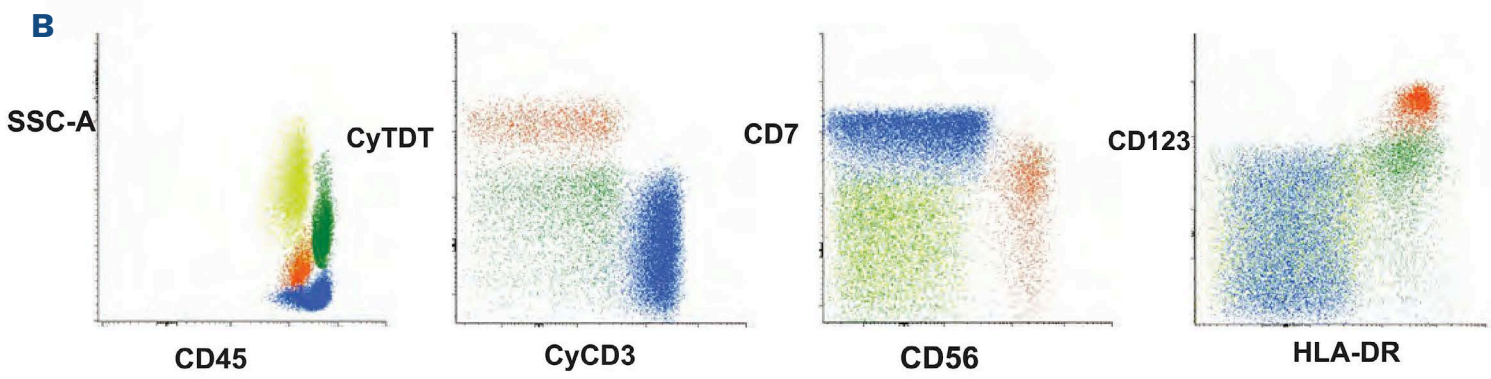
Pediatric BPDCN is typically treated with ALL-like multiagent chemotherapy, including intrathecal CNS prophylaxis; radiotherapy is generally avoided.[2,4] In our cohort, 16/17 evaluable patients received ALL-like therapy (vene-

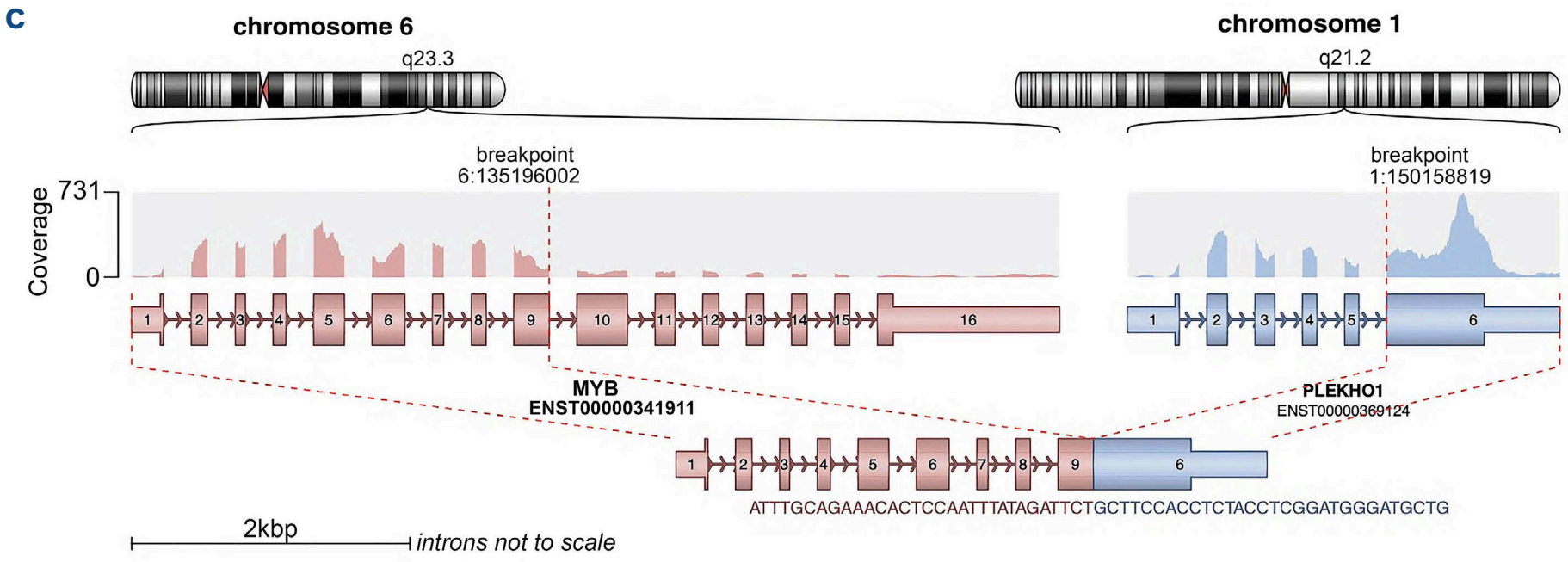
Table 1. Site-stratified clinical characteristics of pediatric blastic plasmacytoid dendritic cell neoplasm.

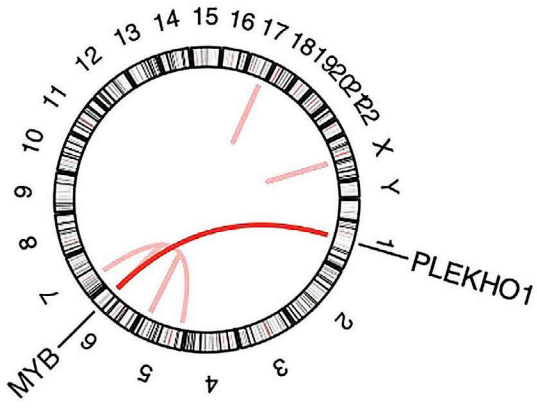
Characteristics	Overall cohort	Skin-only	Skin + systemic	Systemic-only
Patient, N	21	3	8	4
Age at diagnosis, years, median (range)	12 (5-18)	7 (6-12)	14 (6-18)	13 (7-16)
Gender, male, N/N (%)	12/21 (57)	3/3 (100)	5/8 (62)	2/4 (50)
Initial BM involvement, N/N (%)	9/16 (56)	0/3 (0)	5/7 (71)	4/4 (100)
Initial LN involvement, N/N (%)	8/14 (57)	0/3 (0)	6/8 (75)	2/3 (66)
CNS involvement, N/N (%)	5/11 (45)	0/2 (0)	3/5 (60)	2/3 (66)
Remission during therapy, N/N (%)	17/17 (100)	3/3 (100)	7/7 (100)	4/4 (100)
Relapse, N/N (%)	2/16 (12)	0/3 (0)	0/7 (0)	2/3 (66)
ALL-type therapy, N/N (%)	16/17 (94)	3/3 (100)	7/7 (100)	3/4 (75)
Hematopoietic stem cell transplant, N/N (%)	2/17 (12)	1/3 (33)	1/7 (14)	0/4 (0)
Alive at last follow-up, N/N (%)	15/17 (88)	3/3 (100)	6/7 (86)	3/4 (75)
Follow-up, months, median (range)	48 (5-168)	12 (5-168)	17 (8-132)	35.5 (17-108)
MYB/peri-*MYB/MYBL1* rearrangement among informative tumors, N/N (%)	11/12 (92)	2/2 (100)	4/5 (80)	2/2 (100)

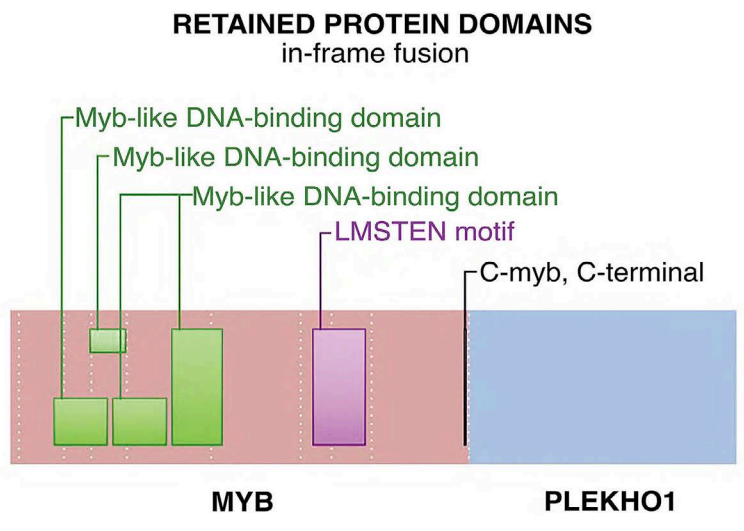
Denominators (N) reflect cases with available data. Site-stratified columns include the 15 sufficiently staged cases described in the text. ALL: acute lymphoblastic leukemia; BM: bone marrow; CNS: central nervous system; LN: lymph node.











SUPPORTING READ COUNT

Split reads in MYB = 1

Split reads in PLEKHO1 = 4

Discordant mates = 0

Continued on following page.

Figure 1. Clinical, histological, and immunohistochemical findings of a skin tumor with concurrent bone marrow histology and flow cytometry immunophenotypic findings. (A) Clinical photograph of a cutaneous lesion in a 17-year-old male with no significant past medical history, presenting with a progressively enlarging, mobile mass on the left lower extremity measuring approximately 6.0 × 6.0 cm. The lesion was non-draining at presentation. Excisional biopsy demonstrated cutaneous involvement by blastic plasmacytoid dendritic cell neoplasm (BPDCN). The dermis is diffusely infiltrated by immature neoplastic cells with blastoid morphology, extending from the superficial to the deep dermis with involvement of the subcutis, while the epidermis is spared (skin; hematoxylin and eosin, ×40 and ×400). Immunohistochemistry shows tumor cell expression of TCL1, CD123, and TCF4 (×400). Bone marrow involvement by BPDCN. Wright-Giemsa-stained aspirate smears demonstrate neoplastic cells with lightly basophilic, agranular cytoplasm and blastoid nuclei with open chromatin and a prominent nucleolus (×600). The bone marrow biopsy (trephine) shows diffuse infiltration by tumor cells (hematoxylin and eosin, ×400). (B) Flow cytometry immunophenotyping in bone marrow aspirate shows neoplastic cells (red) with bright CD45 expression on CD45 expression/side scatter plots. Neoplastic cells are positive for HLA-DR, CD123, CD56, CD7, and CyTdT, and negative for CyCD3. (C) Schematic representation of the *MYB*::*PLEKHO1* fusion. The fusion results from juxtaposition of *MYB* on chromosome 6 (breakpoint: chr6:135,196,002) and *PLEKHO1* on chromosome 1 (breakpoint: chr1:150,158,819). The predicted fusion protein retains the *MYB* DNA-binding domain (green) and the LMSTEN motif (purple).

toclax added in 3), and one received an acute myeloid leukemia (AML)-like regimen; no patient received frontline tagraxofusp. All evaluable patients achieved remission; however, two relapsed, both had systemic-only presentation at diagnosis (cases 5 and 17). Case 17 relapsed after AML-like therapy and died of progressive disease. Case 5 developed early CNS and bone marrow relapse, was refractory to venetoclax-based salvage, CD123-directed cellular therapy, and tagraxofusp. Sequencing of relapse bone marrow identified an acquired *TP53* variant. One additional patient discontinued therapy but was alive at last contact. Outcome data were available for 17 patients: 15 were alive at last follow-up, one died of progressive disease, and one died of treatment-related infection; four additional cases lacked adequate follow-up. Thirteen patients remained alive and event-free at a median follow-up of 48 months (range, 5-168), consistent with prior reports of more favorable outcomes in pediatric BPDCN compared with adult BPDCN.[2,4]

Similarly, published pediatric cases with evaluable bone marrow status and outcomes (*Online Supplementary Table S2*) suggested that bone marrow involvement was associated with adverse outcomes, although these differences did not reach statistical significance (relapse: 7/14 [50%] *vs*. 1/6 [16.7%]; *P*=0.324; death: 6/16 (37%) *vs*. 0/8 (0%); *P*=0.066). In contrast, no relapses or deaths were reported among patients with skin-only disease. Molecular findings among refractory or deceased cases were heterogeneous (including *MYB*-fusion-only disease and cases with additional cooperating lesions), limiting inferences about genotype-specific risk. Cases with bone marrow involvement demonstrated a broader spectrum

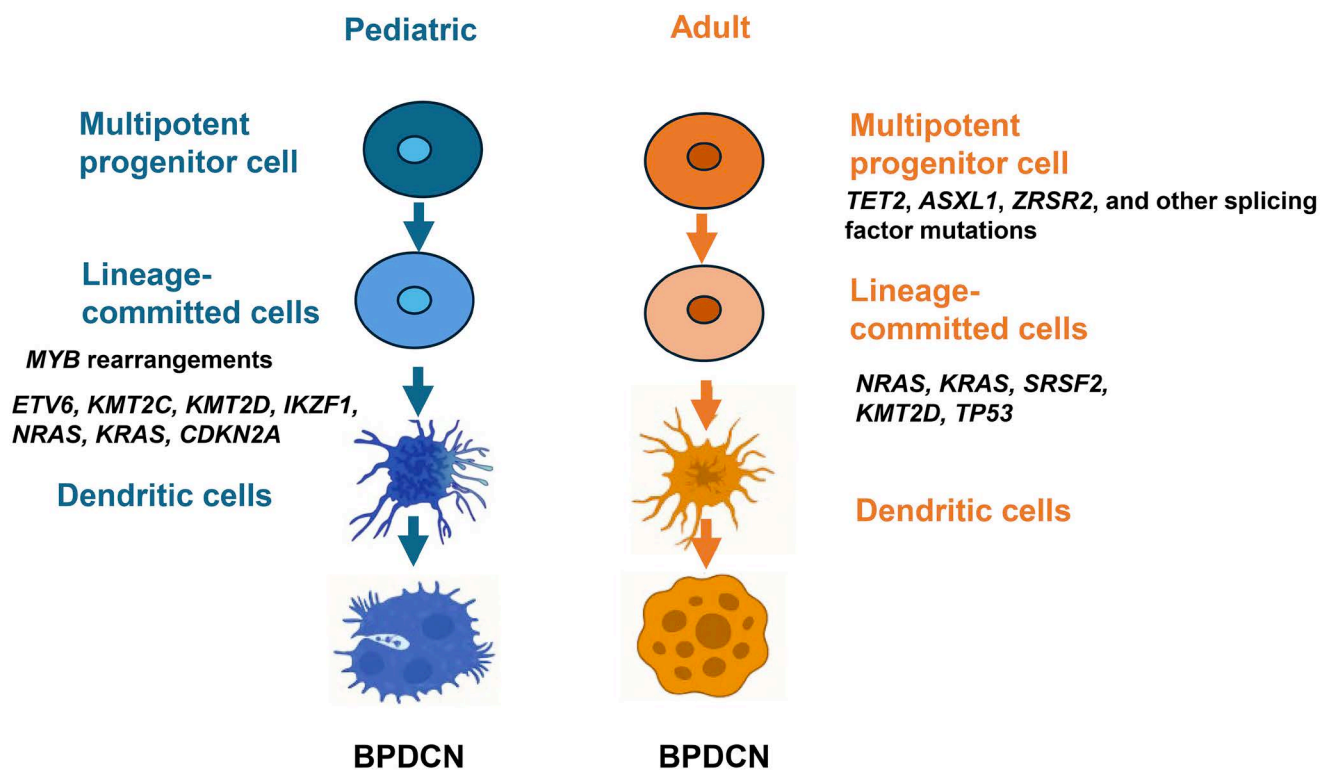


Figure 2. Conceptual model of the molecular evolution of pediatric versus adult blastic plasmacytoid dendritic cell neoplasm. This schematic summarizes published observations indicating that adult blastic plasmacytoid dendritic cell neoplasm (BPDCN) frequently harbors mutations associated with clonal hematopoiesis (e.g., *TET2, ASXL1, ZRSR2*, and other splicing factors) and may share a clonal origin with myeloid neoplasms. In contrast, pediatric BPDCN is predominantly characterized by *MYB*-region rearrangements with fewer recurrent cooperating lesions. This model is hypothesis-generating and is not directly derived from the present cohort.[3,12,14,15]

of cooperating alterations (e.g., *KMT2C/KMT2D* or *ETV6/TET2*) in addition to *MYB* fusions. In contrast, bone marrow-negative, skin-predominant cases more often exhibited *MYB*-driven disease with fewer additional alterations or lesions, such as *KMT2/IKZF* family genes. Outcomes in these cases, including those with cooperating *RAS*-pathway mutations, were generally favorable, although staging and follow-up were heterogeneous.

In adult BPDCN, activated signaling lesions – including *RAS*-pathway mutations – are enriched in patients with systemic involvement, and overt marrow involvement (≥5% BPDCN in bone marrow) is independently associated with inferior overall survival. In this context, *NRAS* appears to track with systemic disease/organ involvement rather than serving as a stand-alone risk marker.[13,14] *TP53* alterations appear uncommon across cohorts (e.g., ~4% in a 50-case clinical cohort);[14] however, integrative profiling suggests that *TP53* represents a key lesion shared between BPDCN and AML, but not chronic myelomonocytic leukemia, and may exert transcriptomic "trans" effects that shape malignant programs, consistent with a higher-risk, AML-like biology (Figure 2).[12,14,15]

In our pediatric BPDCN cohort, *NRAS/KRAS* alterations were relatively frequent and observed across involved anatomic sites, supporting their role as common cooperating events rather than primary drivers. Despite this, relapse and refractory disease were uncommon. Notably, the only patient with early relapse harbored multiple high-risk genomic features at diagnosis, including an *ETV6* rearrangement, deletions of *CDKN2A* and *CDKN2B*, an *RB1* mutation, and a high-variant allele frequency *TP53* alteration, suggesting a more complex, higher-risk biology. These findings indicate that, in contrast to adult BPDCN, *RAS*-pathway mutations in pediatric disease were not clearly associated with adverse outcomes, whereas composite genomic disruption – particularly involving *TP53* – may be associated with aggressive clinical behavior. However, given the limited sample size, these observations should be interpreted with caution.

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https://doi.org/10.3324/haematol.2026.300903

Received: March 17, 2026.
Accepted: April 29, 2026.
Early view: May 7, 2026.

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Disclosures

No conflicts of interest to disclose.

Contributions

RCR, JMK, MTN, NP, and MK conceptualized the study. MK, JRB, MTN, and JLM collected data. JLM, JM, ZC, and KDJ curated molecular data. ZC and MKE conducted formal analysis. MK, ZC, and LK created figures. RCR provided resources. MK and RCR wrote the initial draft, and all co-authors reviewed and revised the manuscript.

Acknowledgments

The authors thank the members of the Anatomic and Neuropathology Translational Support Laboratory (Christina A. Tucker; Nesha Dorsey; Julie Jeschke), the molecular pathology laboratory (Paul Conn, Jiali Gu, Becky Wallace), and the Center for Applied Bioinformatics (Ti-Cheng Chang) at St. Jude Children's Research Hospital.

Funding

This work was funded by the American Lebanese Syrian Associated Charities of St. Jude Children's Research Hospital.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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