Dual Expression of TCF4 and CD123 Is Highly Sensitive and Specific For Blastic Plasmacytoid Dendritic Cell Neoplasm

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汇报人：颜临丽

母细胞性浆细胞样树突状细胞肿瘤 (blastic plasmacytoid dendritic cell neoplasm, BPDCN)

- 定义： BPDCN是一种临床上呈侵袭性的肿瘤，瘤细胞来自浆细胞样树突状细胞的前体细胞（也称为浆样单核细胞）。本病侵犯皮肤与骨髓，白血病性播散的发生率很高
- 流行病学：罕见，可发生于任何年龄，多见于老年人，男/女=3.3
- 病因学：不明，与EB病毒无关
- 部位：本病倾向多部位侵犯，偏嗜皮肤（几乎100%的病例），其次为骨髓和外周血（60%-90%），以及淋巴结（40%-50%）

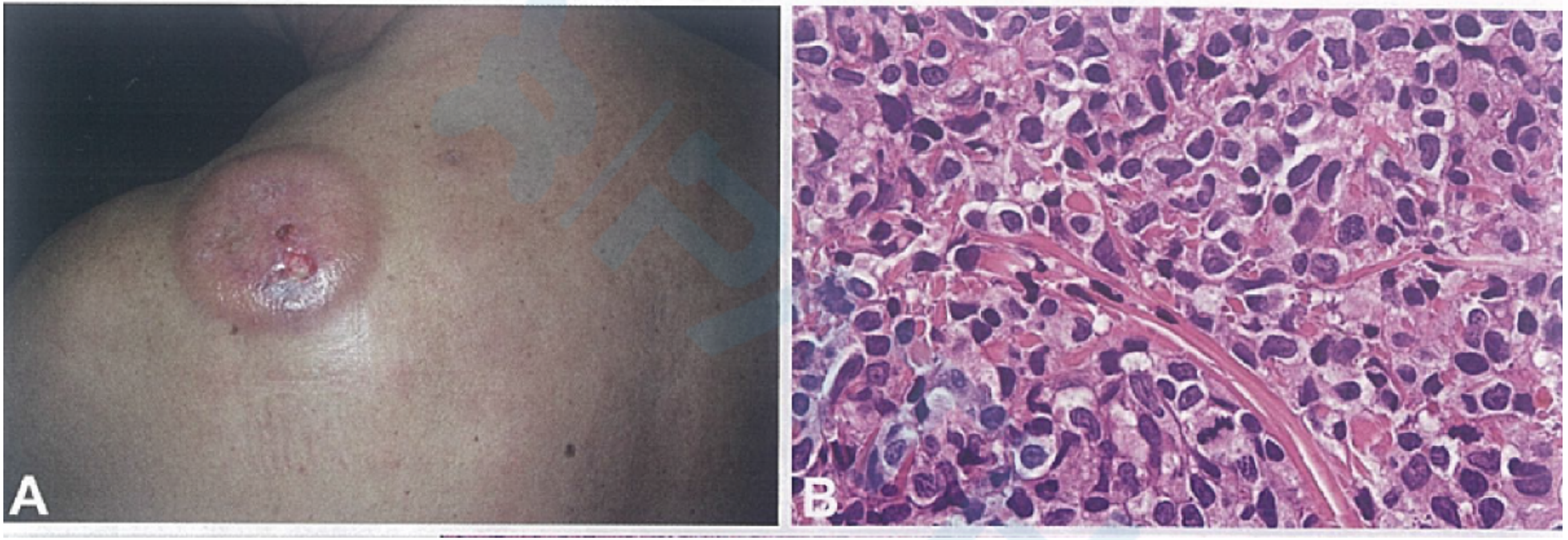
BPDCN

- 临床表现：通常表现为无症状孤立或多发皮损，可呈结节、斑块会瘀斑样。初诊局部淋巴结肿大常见（20%），外周血和骨髓累及轻微，但随着疾病进展必然发生侵犯，大多数病例最终发生明显的白血病期。

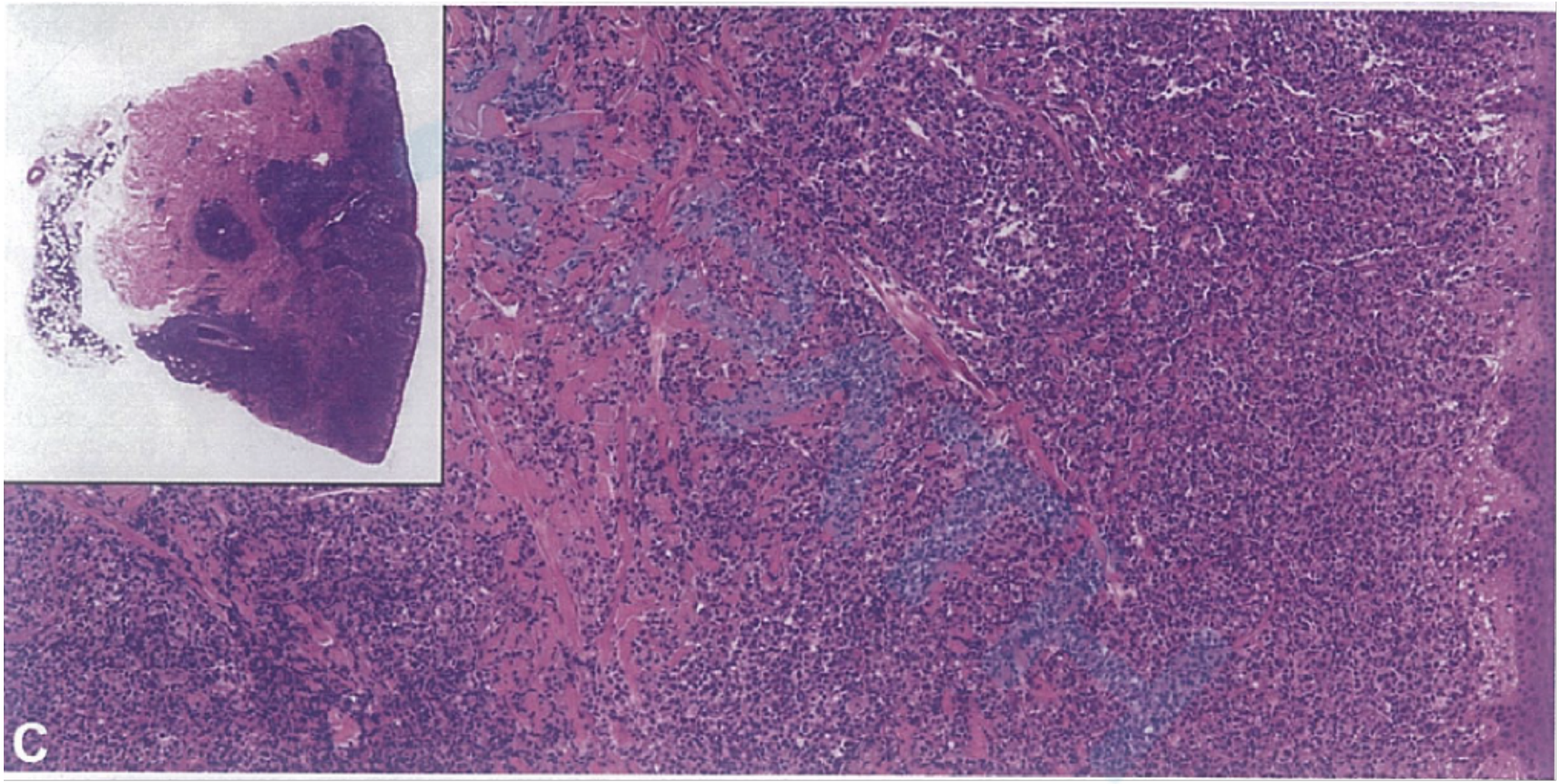
BPDCN

- 形态学：由中等大小的母细胞弥漫性单一性浸润，瘤细胞核不规则，染色质细致，一至数个小核仁。Giemsa染色通常胞浆稀少，灰蓝色，无颗粒。
- 核分裂象多少不定，KI67增殖指数约20-80%。
- 无血管侵犯和凝固性坏死。
- 皮肤：主要侵犯真皮，而不侵犯表皮，但最终扩展至皮下脂肪层。

淋巴结：弥漫性侵犯滤泡间区和髓质区，呈白血病性浸润模式，而淋巴滤泡不受累



A皮肤肿瘤和斑块
B瘤细胞中等大小，核染色质细腻，胞质稀少，提示为未分化母细胞



肿瘤弥漫性浸润真皮并扩展至皮下脂肪组织，但不侵犯表皮

BPDCN

- 免疫表型：

-肿瘤细胞表达CD4、CD43、CD45RA、CD56和浆细胞样树突状细胞相关抗原CD123、CD303、TCL1、CD2AP、SPIB。

-50-80%的病例表达CD68，在细胞质中呈小点状阳性

-约1/3病例表达TdT,阳性细胞范围在10%-80%，CD34和CD117为阴性

-细胞毒性分子如穿孔素和TIA-1大多为阴性

- 预后：临床过程是侵袭性的，中位存活时间12-14个月

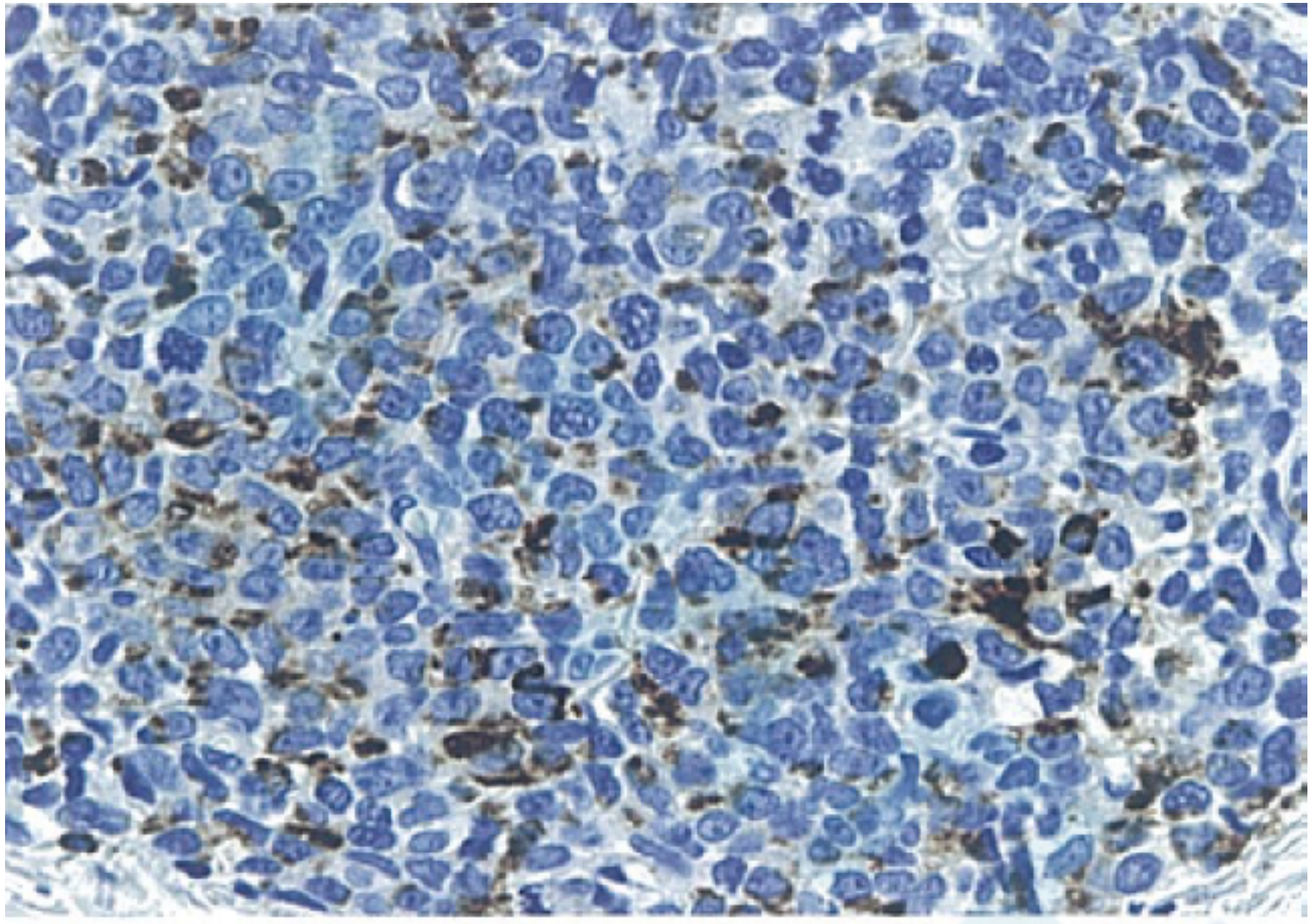


Fig 9.03 Blastic plasmacytoid dendritic cell neoplasm The neoplastic cells show immunoreactivity for CD68 ir the form of small perinuclear dots.

BACKGROUND

CD123 and CD303

- High-level CD123 expression is a defining feature of BPDCN, but this finding generally lacks specificity due to the common expression of CD123 in AML and other hematopoietic precursors of plasmacytoid dendritic cells (pDCs), its expression is often aberrantly downregulated in BPDCN thus limiting its sensitivity.

CD123:敏感而不特异
CD303：特异而不敏感

TCF4

- TCF4, previously known as SL3-3 enhancer factor 2 (SEF2) and immunoglobulin transcription factor 2 (E2-2), is a basic helix-loop-helix protein that was first described as a B-lineage specific enhancer
- TCF4 is a member of the E-box Tcf/Lef family of transcription factors, downstream effectors of the Wnt signaling pathway, and has been identified as a key regulator controlling the committed development of pDCs from common dendritic cell progenitors through a regulatory network of secondary transcription factors

TCF4 and BPDCN

- The recent discovery of TCF4 as a master regulator of the BPDCN transcriptional network has provided a novel marker for this disease.
- Strong and homogenous TCF4 expression has been shown by immunohistochemistry in BPDCN cases.

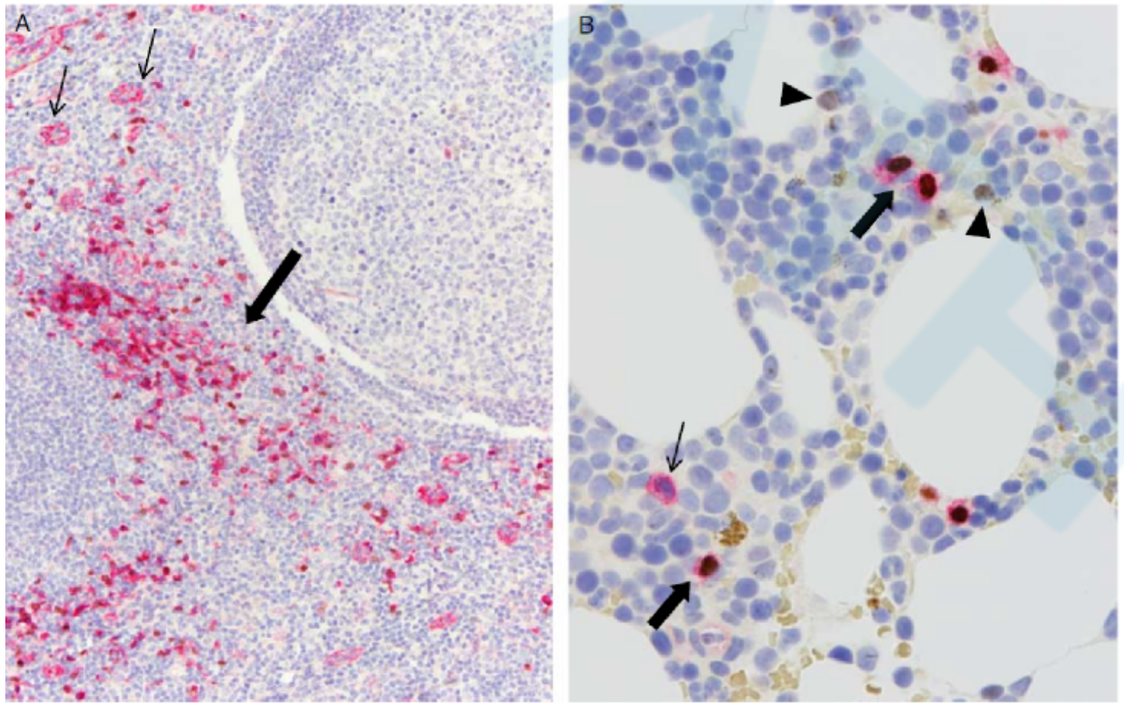
- we developed a dual-color TCF4/CD123 immunohistochemical stain to survey a large cohort of BPDCN cases and potential BPDCN mimics for to determine the analytic characteristics of this marker combination in a practical clinical context.

MATERIALS AND METHODS

- Study Group(48 confirmed BPDCN cases, 464 non-BPDCN cases)
- Immunohistochemistry(dual-color TCF4/CD123 immunohistochemistry stains)

scattered pDCs in tonsil tissue

- homogenous strong TCF4 (nuclear; brown)
- Colocalized CD123 (membranous; red) staining



semi-quantitatively :H-score

- intensity(negative =0; weak =1; moderate = 2; strong= 3),
- extent (number of positive cells per 5000 cells evaluated manually),
- The H-score was defined as the product of the intensity score and staining extent.

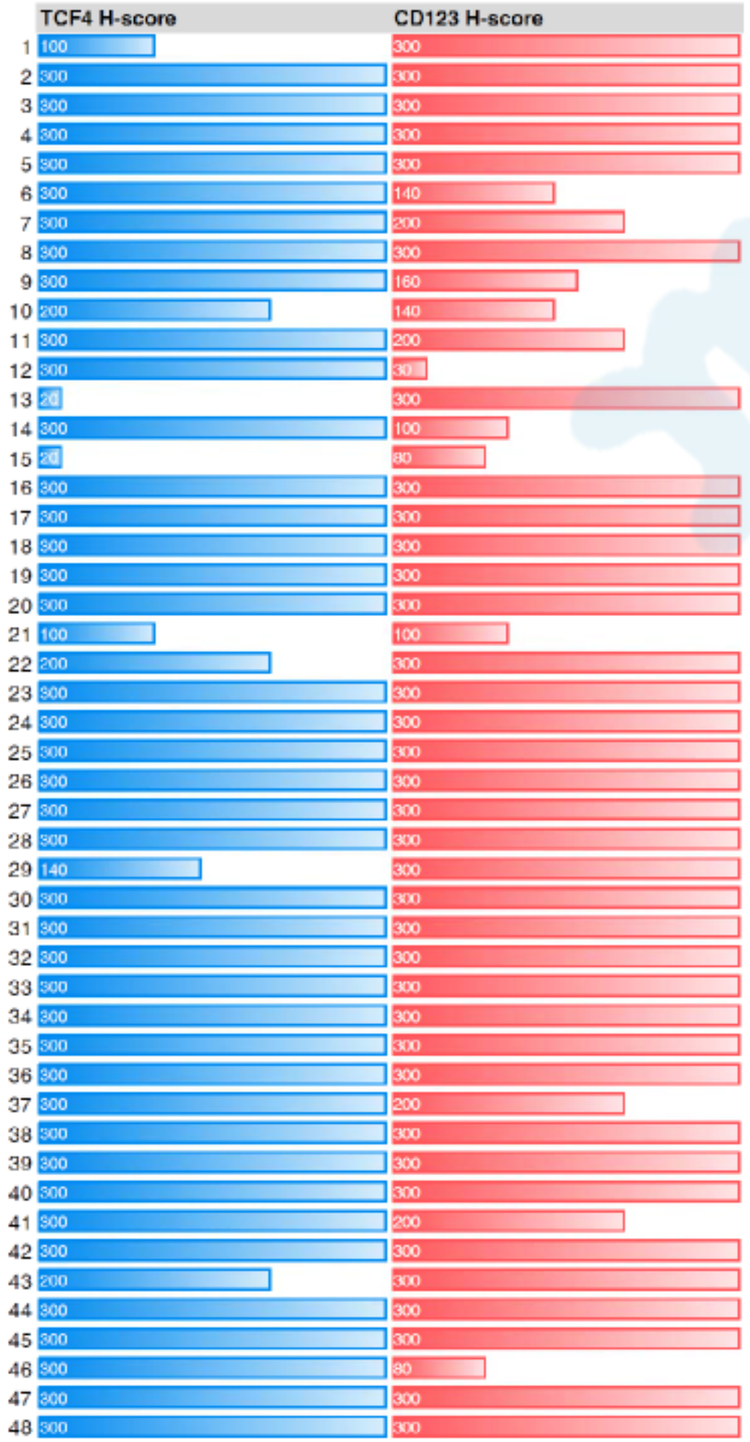
- Flow Cytometry (BPDCN cases)
- Statistical Analysis

RESULTS

Staining Characteristics of TCF4/CD123 Dual-color Immunostain in BPDCN Cases

TABLE 1. BPDCN Group Immunohistochemistry/Flow Cytometry Results

Markers	Positive Expression, n/N (%)
TCF4/CD123	48/48 (100)
BCL2	9/9 (100)
CD2	10/28 (42.3)
CD22	0/11 (0)
CD303	1/11 (9.09)
CD33	15/26 (57.7)
CD4	47/48 (97.9)
CD43	11/11 (100)
CD56	46/48 (95.8)
CD7	21/27 (76)
HLA-DR	35/35 (100)
TCL1	30/41 (97.6)
TdT	13/27 (48.1)



- TCF4 :median H-score was 300(mean =270.4; range, 20 to 300)

- CD123 : median H-score was 300(mean=259; range, 30 to 300)

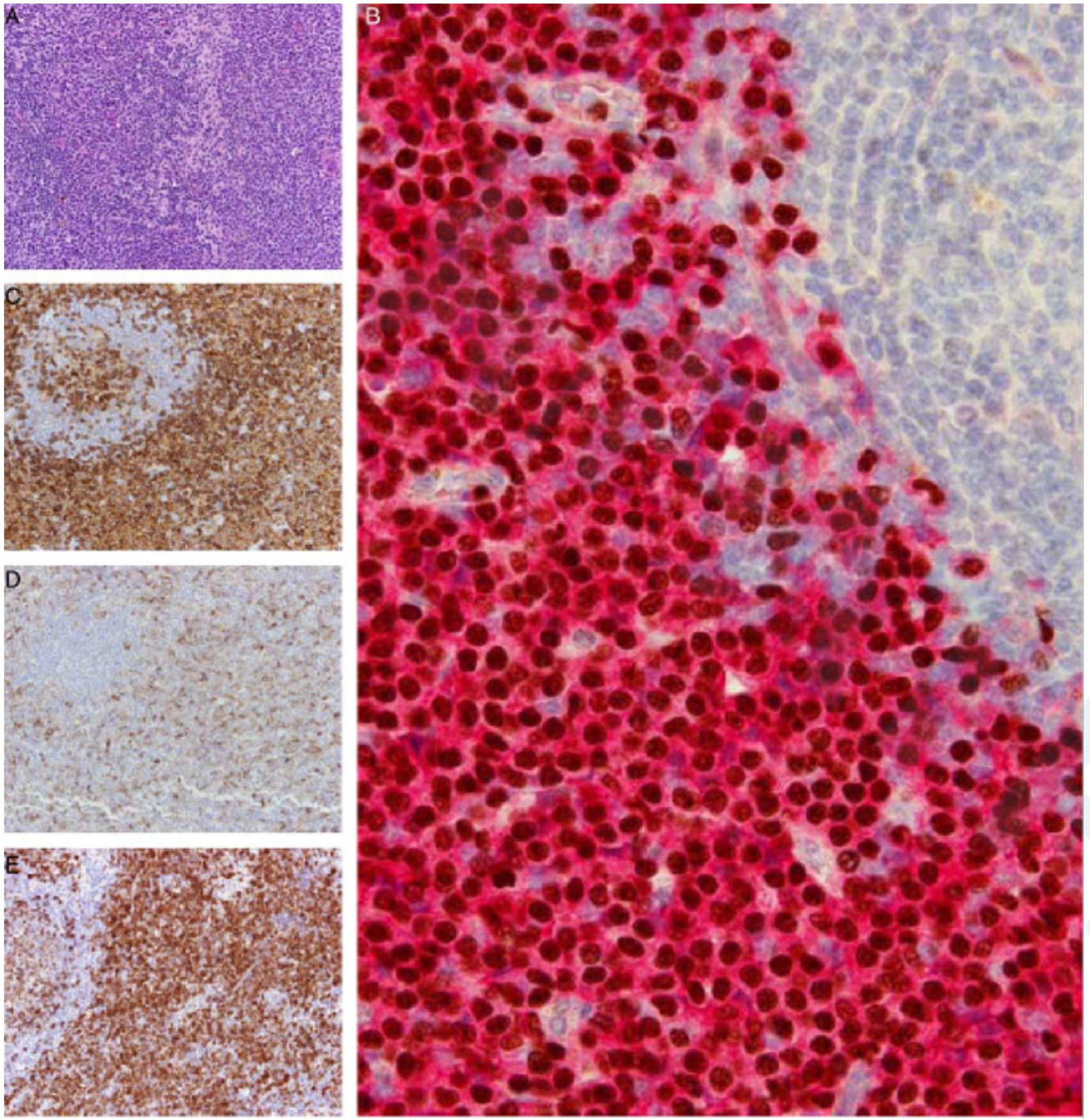


FIGURE 1.
A, BPDCN involving lymph node
B, Dual-color TCF4/CD123 immunohistochemistry demonstratingnuclear TCF4 (brown) and membranous CD123 (red) (immunohistochemistry with hematoxylin counterstain).
C, CD4 immunohistochemistry
D, CD56 immunohistochemistry
E, TCL1 immunohistochemistry

Comparison of TCF4/CD123 Dual-color Immunohistochemistry Staining to Multiparameter Flow Cytometry in Bone Marrow Samples

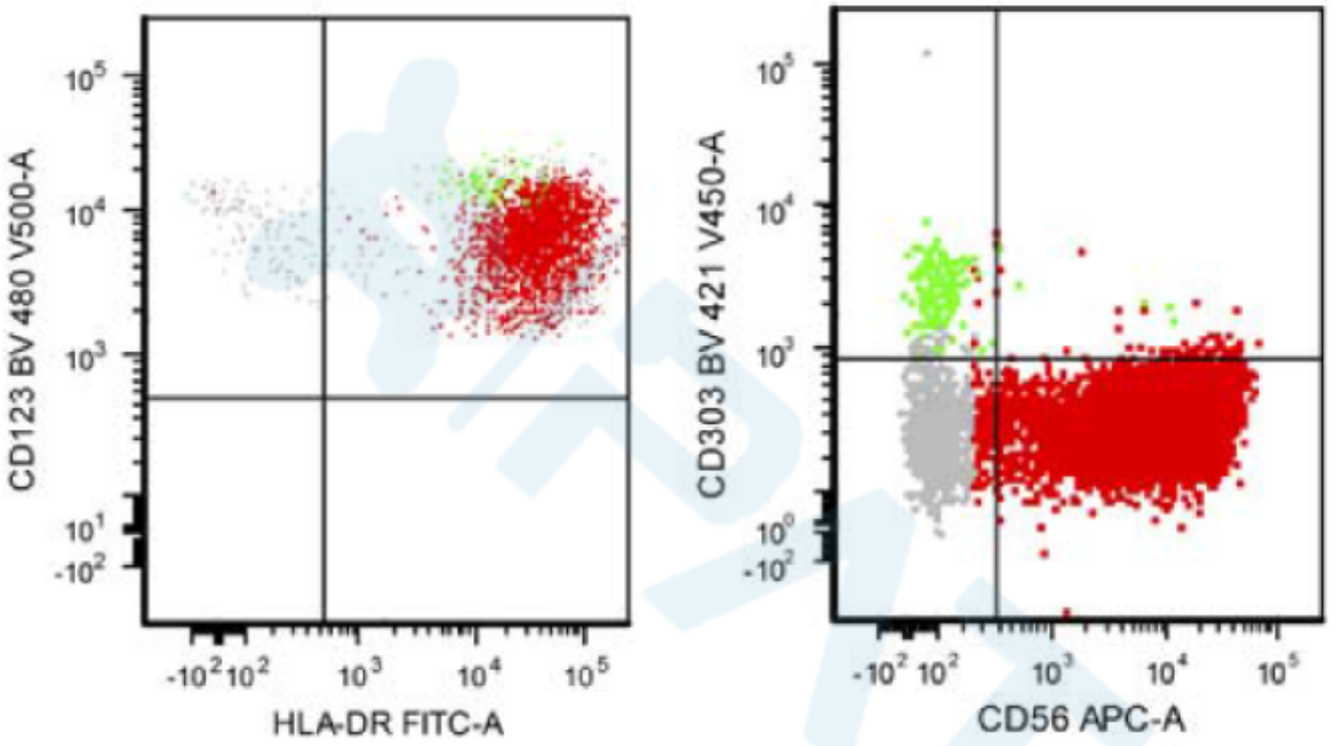


FIGURE 3. Multiparameter flow cytometry immunophenotyping demonstrates blastic plasmacytoid dendritic neoplasm cells (red) with aberrant CD303 loss (right panel). Residual benign pDCs (green) are positive for CD303. Gray: basophils are used as the negative control for CD303.

- CD123 expression by flow cytometry an immunohistochemistry was concordant
- In contrast, 10/11 (90.9%) BPDCN cases showed aberrantly negative CD303 expression。In each of these cases, BPDCN cells exhibited dual TCF4/CD123 expression with a TCF4 H-score of 300.

Staining Characteristics of TCF4/CD123 Dual-color Immunohistochemistry in Non-BPDCN Tissues

TABLE 2. Immunohistochemistry Detection of TCF4/CD123 Expression by Neoplastic Cells in Cancers Other Than BPDCN

Category	$TCF4^+/CD123^+$, n/N (%)	$TCF4^+/CD123^-$ (n*)	$TCF4^-/CD123^+$ (n*)
AML	0/110 (0)	0	0
Adult T-cell leukemia/lymphoma	0/4 (0)	0	0
Anaplastic large cell lymphoma, anaplastic lymphoma kinase-negative	0/5 (0)	0	0
Anaplastic large cell lymphoma, anaplastic lymphoma kinase-positive	0/5 (0)	0	0
Angioimmunoblastic T-cell lymphoma	0/5 (0)	0	0
Angiosarcoma†	0/3 (0)	0	0
Atypical fibroxanthoma	0/3 (0)	0	0
B-ALL	1/23 (4.3)	7	3
Chronic lymphocytic leukemia/small lymphocytic lymphoma	0/8 (0)	6	0
CMML	0/91 (0)	0	0
Classical Hodgkin lymphoma	0/5 (0)	0	0
Diffuse large B-cell lymphoma	0/44 (0)	3	1
Extranodal marginal zone lymphoma	0/5 (0)	0	0
Follicular lymphoma	0/5 (0)	0	0
Hairy cell leukemia	0/6 (0)	0	2
Hepatosplenic T-cell lymphoma	0/5 (0)	0	0
Kaposi sarcoma†	0/3 (0)	0	0
Langerhans cell histiocytosis	0/5 (0)	0	0
Leiomyosarcoma†	0/1 (0)	0	0
Lymphoplasmacytic lymphoma	0/5 (0)	0	0
Malignant fibrous histiocytoma†	0/1 (0)	0	0
Mantle cell lymphoma	0/10 (0)	0	0
Malignant melanoma	0/3 (0)	0	0
Merkel cell carcinoma	0/3 (0)	1	0
Monomorphic epitheliotropic T-cell lymphoma	0/5 (0)	0	0
Mycosis fungoides	0/5 (0)	0	1
Myelodysplastic syndrome	0/22 (0)	0	0
Myeloproliferative neoplasm	0/44 (0)	1	1
Natural killer/T-cell lymphoma, nasal type	0/3 (0)	0	0
Nodal marginal zone lymphoma	0/6 (0)	0	0
Nodular lymphocyte predominant Hodgkin lymphoma	0/5 (0)	0	0
Peripheral T-cell lymphoma, not otherwise specified	0/5 (0)	0	0
Splenic marginal zone lymphoma	0/2 (0)	0	0
Squamous cell carcinoma†	0/4 (0)	0	0
Subcutaneous panniculitis-like T-cell lymphoma	0/5 (0)	0	0
T-lymphoblastic leukemia/lymphoma	0/3 (0)	0	0
T-cell large granular lymphocytic leukemia	0/5 (0)	0	0
T-cell prolymphocytic leukemia	0/5 (0)	0	0

*Number of cases with H-score ≥ 20.
†Cutaneous.

- 1 case of B-ALL, negative for BCR/ABL1 fusion, had TCF4/CD123 coexpression (1/477; 0.2%), with H-scores of 200 for both markers. The neoplastic cells definitively expressed the B-lineage markers CD19 and CD22, thus excluding BPDCN as a consideration.

TABLE 3. Analytic Performance of Dual-color TCF4/CD123 Immunohistochemistry in the Diagnosis of BPDCN

	Value (%)	95% Confidence Interval
Sensitivity	100	92.6%-100.0%
Specificity	99.8	98.8%-99.9%
Positive predictive value	98.0	87.1%-99.7%
Negative predictive value	100	NA
Accuracy	99.8	98.9%-100.0%

NA indicates not available.

The use of dual-color TCF4/CD123 immunohistochemistry provided significant advantages over either marker alone

DISCUSSION

CD123 expression

- Hematologic malignancies,

-AML,

-lymphoblastic leukemia/lymphoma,

-hairy cell leukemia,

-myeloproliferative neoplasms

-and in occasional lymphoid malignancies

TCF4 expression

- various types of cancer, including squamous cell carcinoma, prostate and colorectal cancer,
- AML, lymphoblasticleukemia/lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma.
- Merkel cell carcinoma

TCF4/CD123 coexpression

- BPDCN
- pDCs (precursors of plasmacytoid dendritic cells)
- Mature pDC proliferation, increased numbers of pDCs in various neoplastic and non-neoplastic diseases (CMML、Hodgkin lymphoma)

supplementing the stain with other markers of pDC aberrancy, such as CD56, Ki-67 or TdT

summary

- dual-color TCF4/CD123 immunohistochemistry provides a sensitive and specific cost effective standalone diagnostic marker of BPDCN and a useful general pDC marker in tissue samples.