

A Rare Case Report of Blastic Plasmacytoid Dendritic Cell Neoplasm

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Abstract Blastic plasmacytoid dendritic cell neoplasm also formerly known as Blastic NK cell lymphoma is a very rare haematological malignancy. WHO defined BPDCN as a neoplasm with features of cutaneous lymphoma and/or leukaemia and designated BPDCN in a separate category under the myeloid class of neoplasms since 2008. Diagnosis of BPDCN requires both morphological evidence of plasmacytoid dendritic blast cells and immunohistochemical positivity for CD123, CD4, CD56 and TLC-1. Unlike other haematological malignancies there are no established optimal chemotherapy regimens for BPDCN although standard chemotherapeutic regimens used for induction treatment of AML, ALL and high grade lymphoma have shown complete remission rates albeit for a short duration, with ALL regimens having a higher remission percentage among both adults and children. Here we present a case of BPDCN without skin involvement.

Keywords: BPDCN, pathological features, Immunohistochemical criteria, prognosis, chemotherapy role

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1. Introduction

Tauchi et al initially described this entity as a possible histiocytic/monoblastic leukaemia in 1990, which was later reported in 1994 (Adachi et al) as a CD4/CD56/N-CAM positive cutaneous lymphoma with a unique agranular morphology and phenotype [1]. After multiple nomenclatures over the years, WHO finally described the entity in 2008 as Blastic plasmacytoid dendritic cell neoplasm after the discovery that BPDCN is derived from clonal proliferation of precursors of plasmacytoid dendritic cells and later gave it an independent classification of a medullary tumour in the WHO classification of haematological tumour [2].

The exact incidence and prevalence of BPDCN is not known in view of the lack of precise diagnostic criteria prior to 2008 and has an estimated approximate incidence of 0.44% of all the haematological malignancies (Bruno et al 2004) and 0.7% of all cutaneous lymphomas (Ng et al 2006). However the true incidence could be underestimated because a small but significant proportion of patients (approximately <1% of acute leukaemia cases-Jacob et al 2003) present with a pure leukemic involvement without skin lesions making diagnosis furthermore difficult [3]. BPDCN predominantly affects males of all races and geographical distribution with an approximate sex ratio of 3:1 [4]. Most patients, approximately 80% present with cutaneous lesions (bruise like patches, plaques, nodules, tumour) with or without

bone marrow involvement and leukemic dissemination. However a minority of the patients present with leukaemia without skin lesions. Approximately 10-20 % of the patients with BPDCN may have a history of haematological malignancy such as MDS, Chronic/Acute Myeloid leukaemia or Chronic myelomonocytic leukaemia [5,6].

Here we present a case report of BPDCN without skin lesions.

2. Case Report

A 41 years old male patient had initially presented with the complaints of intermittent fever, generalized fatigue, pancytopenia and was evaluated. Bone marrow Aspirate and biopsy showed infarcted marrow with scant atypical mononuclear cells. (CD 68 positive in atypical cells and MPO positive). Ultrasound Abdomen showed hepatomegaly with diffuse fatty infiltration and borderline splenomegaly. CT scan of the chest showed a micronodule in the posterior segment of the right upper lobe with subpleural and subsegmental atelectasis in right lower lobe. He became symptomatically better after multiple transfusions, antibiotics, antifungals and was on regular follow up with bone marrow evaluations which showed normal trilineage haematopoiesis. He presented five months later with complaints of left axillary mass and was further evaluated. PET CT showed multiple enlarged and mildly hypermetabolic lymph nodes in the left submandibular region, bilateral axilla, paraaortic, aortocaval, bilateral iliac and bilateral inguinal region.

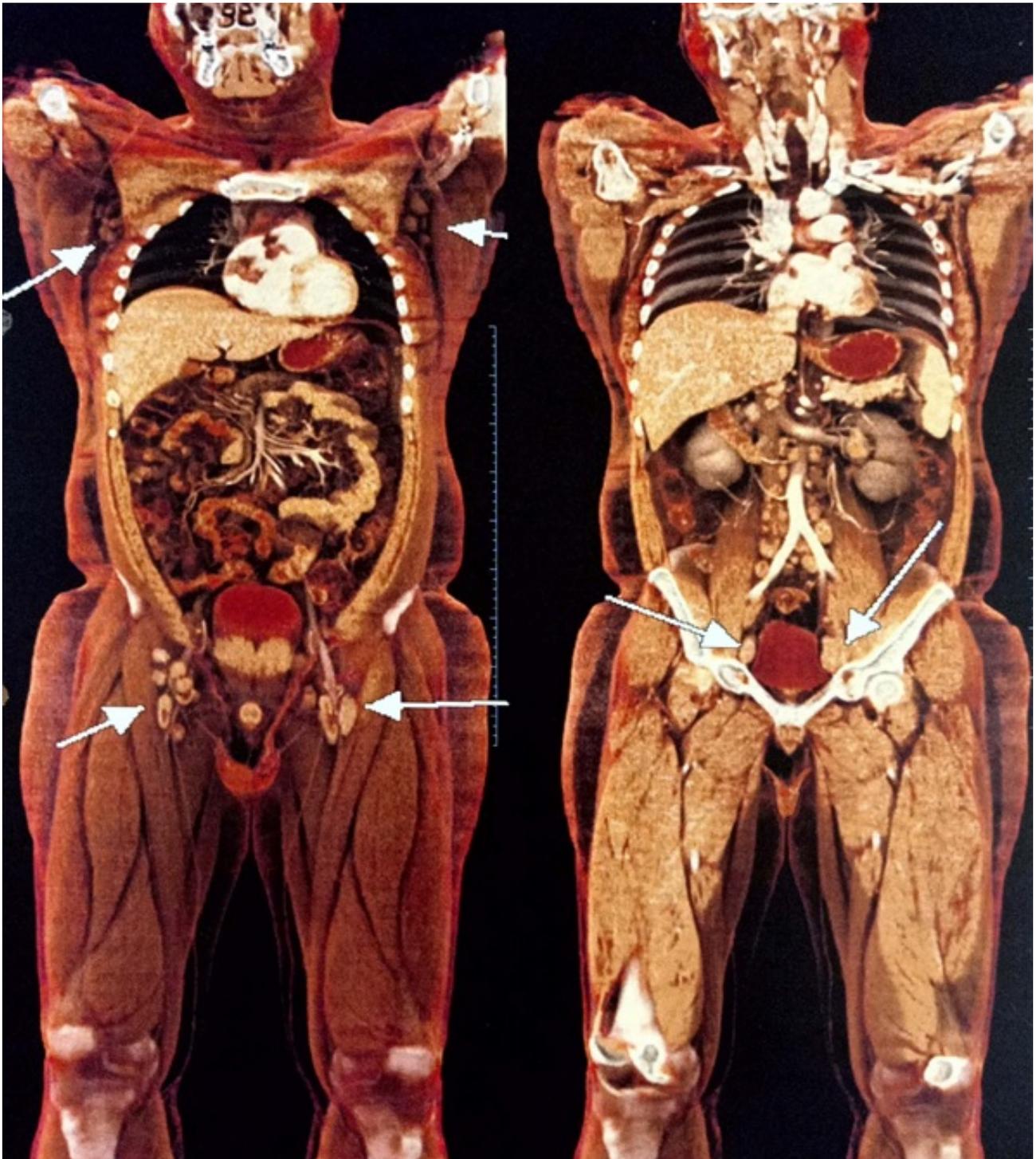


Figure 1. PET CT at diagnosis

Hypermetabolism in the marrow of proximal humeri and femora with no evidence of hypermetabolism in the spleen. Biopsy and IHC of the left axillary nodes showed features suggestive of hemolymphoid malignancy with monocytic/histiocytic lineage (Ki 67 - 70 to 80%, CD4, CD56, CD 79a, CD 2, CD5, CD7, CD8, CD 43, CD 68, LCA and MPO -positive. CD 123 - negative). Flow cytometry reported that the absence of lineage associated markers with classic phenotype of CD4/CD56 /CD123 /CD45 expression and aberrant CD33 is indicative of Blastic plasmacytoid dendritic cell neoplasm. He was started on chemotherapy with Hyper CVAD Regimen after flow cytometry reports.

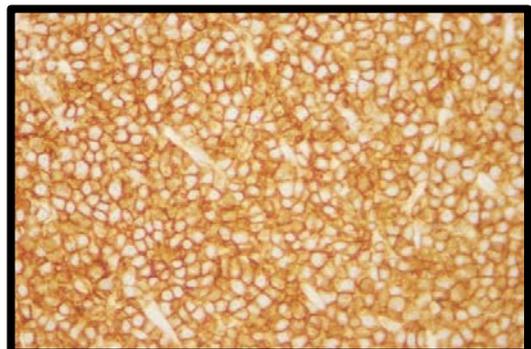


Figure 2. CD 4+

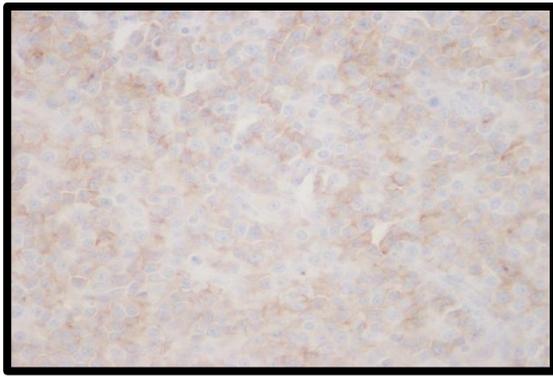


Figure 3. CD 56 +

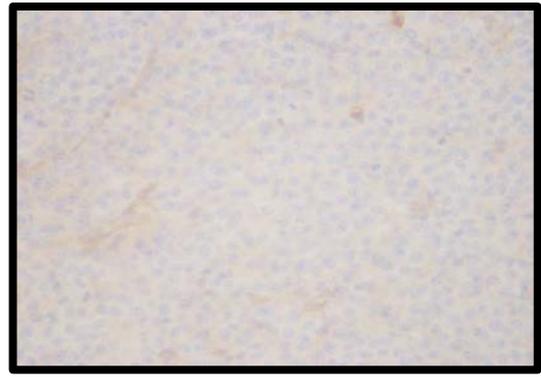


Figure 4. CD 123 +

Follow up PET CT post 4 cycles of HYPER CVAD chemotherapy showed near complete response.



Figure 5. Follow up PET CT showing near complete resolution of bilateral axillary, inguinal, paraaortic, aortocaval and iliac lymphnodes with complete metabolic resolution. Resolution of minimally hypermetabolic left level 2 cervical lymphnodes

3. Discussion

BPCDN is a rare aggressive haematological malignancy affecting elderly patients with a median age of onset between 60-80 years and an overall median survival of approximately 12-20 months from diagnosis [7,8,9], however it can present at any age including paediatric age group where the overall prognosis and long term survival is better than adults. Approximately 80% of BPCDN patients present with cutaneous lesions which may progress to involve multiple sites including peripheral blood, bone marrow, lymph nodes, spleen and rarely the Central nervous system.

The pathogenesis of BPCDN is thought to be due to the malignant transformation of the precursor plasmacytoid dendritic cells with a typical agranular morphology and CD4, CD56 co-expression. BPCDN requires an extensive analysis for a definite diagnosis due to its significant phenotypic, immunohistochemical overlap with other haematological malignancies and heterogeneity in the immunophenotypic clinical profile. Diagnosis is generally based on Immunohistochemistry or flow cytometry detection of one or more of these markers (CD4+, CD56+, CD123+, TCL-1+ and blood dendritic antigen-2(BDCA2)/CD303+) with an absence of lineage specific antigens on tumour cells. Myeloid markers such as CD 33, CD68 and CD43 may also be expressed in BPCDN [10,11,12,13], in particular CD68 antigen typically expressed by granulocytes and histiocytes as well as normal plasmacytoid cells is noted in approximately 50% of the cases. [14]

Majority of BPCDN patients may have chromosomal alterations (approximately 75%)-although none of it specific or diagnostic as it may also be associated with other haematological malignancies. Cytogenetic studies have identified six recurrent deletions of the regions 5q21 or 5q34 (72%), 12p13(64%), 6q23-qter(50%), 15q(43%) and of the entire chromosome 9(28%). [15,16] Inactivation of tumour suppressor genes (RB1, TP53, CDKN2A) and activation of oncogenes (NRAS, KRAS,GTPase) has also been observed in BPCDN. MYC translocations were reported in approximately 39% of BPCDN patients with t(6;8) (p21;q24) being the most commonest type of rearrangement with more aggressive behaviour. [17,18] Clinically MYC positivity was found to have relatively good response to ALL based chemotherapy. [17,19]

Most BPCDN patients present with asymptomatic purpuric, plaque like, nodular or ulcerated skin lesions that can be varied in appearance. However lymphadenopathy, splenomegaly, cytopenia due to bone marrow involvement can also be present at diagnosis with or without skin involvement in a significant proportion of patients. Morphologic review of the peripheral blood may show malignant cells that are diffusely monomorphic, poorly differentiated, medium to large sized blasts with irregular nuclei, fine chromatin, >1 small nucleolus and scant to moderate amount of lightly basophilic cytoplasm with occasional vacuoles localized along the cell membrane and pseudopodia resembling myeloblasts or lymphoblasts. [4,20] In Skin biopsies the dermis and subcutaneous fat are usually massively infiltrated, sparing the epidermis and adnexa [21]. Lymph node biopsies may show significant involvement of the interfollicular areas and medulla, generally sparing B cell follicles. In patients with or

without cutaneous manifestations CT/PET CT imaging can characterize the extent of disease involvement. Jeong et al reported lung involvement in a BPCDN patient visualized by CT scan asserting the need for radiological imaging for early diagnosis and early management.

Considering the rarity and lack of prospective data on treatment of BPCDN, there had been no universally accepted/approved therapeutic approach prior to 2018. Induction chemotherapy regimens like Hyper CVAD have reported to have better response and remission rates although brief (12-20 months) in comparison to standard therapies (CHOP like regimens). A retrospective study by Pemmaraju et al reported a CR rate of 90% with a mean overall survival ranging from 23 months in patients with only cutaneous involvement to 29 months in those with bone marrow involvement at diagnosis. Allogenic Stem cell transplant particularly after first remission may prolong the remission duration and is potentially curative.

Universal positivity for CD123 in BPCDN has led to multiple emerging research opportunities and clinical trials in yielding novel therapeutic approaches like the CD123 directed cytotoxin known as diphtheria toxin interleukin 3 (DT-1L3) later known as SL 401 (tagraxofusp) has shown to achieve an ORR of 90% in frontline setting at a targeted dose of 12micrograms/kg/day IV, day 1-5 on a 21 day cycle with 45% of the patients in frontline setting proceeding to SCT and a 69% ORR in relapsed/refractory setting [22]. Tagraxofusp is associated with a number of side effects like fever, weight gain, liver toxicity, thrombocytopenia, peripheral edema and hypersensitivity reactions. However the most serious complication noticed was capillary leak syndrome which is characterised by hypotension, hypoproteinemia and hemoconcentration. Capillary leak syndrome could be potentially life threatening and requires careful monitoring of body weight, fluid status, blood pressure and serum albumin levels especially before the administration of the first dose. Moreover, the toxicity profile of Tagraxofusp is not age dependant and unlike standard chemotherapy, in the case of this cytotoxin there seems to be no cumulative toxicity in patients as studied by Pemmaraju N et al. [23].

4. Conclusion

BPCDN is a rare aggressive haematological malignancy with phenotypic heterogeneity and variable expression of CD4, CD56 or alternate plasmacytoid markers. It generally has an indolent clinical presentation and poor prognosis. Multidisciplinary approach including clinical, histopathological, radiological and immunophenotypic studies are required for an accurate diagnosis. The recently FDA approved Tagraxofusp -erzs (SL 401) has become the de facto frontline standard of care for patients with BPCDN, offering an alternative to aggressive induction chemotherapy regimens.

Combination therapies with CD123, bispecific CD123 antibodies and other therapy approaches based on novel gene signature studies/novel biological rationale include Venetoclax (BCL2 inhibitors) [24], bortezomib [25], hypomethylator therapies [12], bromodomain and extra terminal domain inhibitors [26,27] have shown

promising clinical activity and may redefine the future therapeutic approach in the management of BPCDN.

References

- [1] Adachi M, Maeda K, Takekawa M, et al. High expression of CD56 (N-CAM) in a patient with cutaneous CD4-positive lymphoma. *Am J Hematol.* 1994; 47(4): 278-282.
- [2] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016; 127(20): 2391-2405.
- [3] Jacob MC, Chaperot L, Mossuz P, et al. CD4+ CD56+ lineage negative malignancies: a new entity developed from malignant early plasmacytoid dendritic cells. *Haematologica.* 2003; 88(8): 941-955.
- [4] Feuillard J, Jacob MC, Valensi F, et al. Clinical and biologic features of CD4(+)CD56(+) malignancies. *Blood.* 2002; 99(5): 1556-1563.
- [5] Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica.* 2013; 98(2): 239-246.
- [6] Brunetti L, Di Battista V, Venanzi A, et al. Blastic plasmacytoid dendritic cell neoplasm and chronic myelomonocytic leukemia: a shared clonal origin. *Leukemia.* 2017; 31(5): 1238-1240.
- [7] Foong HB, Chong M, Taylor EM, Carlson JA, Petrella T. Blastic plasmacytoid dendritic cell neoplasm in an elderly woman. *Med J Malaysia.* 2013; 68(2): 161-163.
- [8] Tsagarakis NJ, Kentrou NA, Papadimitriou KA, et al. Acute lymphoplasmacytoid dendritic cell (DC2) leukemia: results from the Hellenic Dendritic Cell Leukemia Study Group. *Leuk Res.* 2010; 34(4): 438-446.
- [9] Wang H, Cao J, Hong X. Blastic plasmacytoid dendritic cell neoplasm without cutaneous lesion at presentation: case report and literature review. *Acta Haematol.* 2012; 127(2): 124-127.
- [10] Sullivan JM, Rizzieri DA. Treatment of blastic plasmacytoid dendritic cell neoplasm. *Hematology Am Soc Hematol Educ Program.* 2016; 2016(1): 16-23.
- [11] Deotare U, Yee KW, Le LW, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: 10-Color flow cytometry diagnosis and HyperCVAD therapy. *Am J Hematol.* 2016; 91(3): 283-286.
- [12] Laribi K, Denizon N, Besançon A, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm: From Origin of the Cell to Targeted Therapies. *Biol Blood Marrow Transplant.* 2016; 22(8): 1357-1367.
- [13] Lin C, Wu M, Kuo T, Lu P. Cutaneous blastic plasmacytoid dendritic cell neoplasm: Report of a case and review of the literature. *Dermatologica Sinica.* 2017; 35(2): 96-99.
- [14] Riaz W, Zhang L, Horna P, Sokol L. Blastic plasmacytoid dendritic cell neoplasm: update on molecular biology, diagnosis, and therapy. *Cancer Control.* 2014; 21(4): 279-289.
- [15] Petrella T, Dalac S, Maynadié M, et al. CD4+ CD56+ cutaneous neoplasms: a distinct hematological entity? Groupe Français d'Etude des Lymphomes Cutanés (GFELC). *Am J Surg Pathol.* 1999; 23(2): 137-146.
- [16] Leroux D, Mugneret F, Callanan M, et al. CD4(+), CD56(+) DC2 acute leukemia is characterized by recurrent clonal chromosomal changes affecting 6 major targets: a study of 21 cases by the Groupe Français de Cytogénétique Hématologique. *Blood.* 2002; 99(11): 4154-4159.
- [17] Sakamoto K, Katayama R, Asaka R, et al. Recurrent 8q24 rearrangement in blastic plasmacytoid dendritic cell neoplasm: association with immunoblastoid cytology, MYC expression, and drug response. *Leukemia.* 2018; 32(12): 2590-2603.
- [18] Sumarriva Lezama L, Chisholm KM, Carneal E, et al. An analysis of blastic plasmacytoid dendritic cell neoplasm with translocations involving the MYC locus identifies t(6;8)(p21;q24) as a recurrent cytogenetic abnormality. *Histopathology.* 2018; 73(5): 767-776.
- [19] Boddu PC, Wang SA, Pemmaraju N, Tang Z, Hu S, Li S, Xu J, Medeiros LJ, Tang G. 8q24/MYC rearrangement is a recurrent cytogenetic abnormality in blastic plasmacytoid dendritic cell neoplasms. *Leuk. Res.* 2018; 66, 72-78.
- [20] Swerdlow SH, Camo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editors. World health organization classification of tumours. 4th ed. International Agency for research on cancer, Lyon, France 2017.
- [21] Cota C, Vale E, Viana I, et al. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm—morphologic and phenotypic variability in a series of 33 patients. *Am J Surg Pathol.* 2010; 34(1): 75-87.
- [22] Pemmaraju N, Sweet K, Lane A et al. Results of pivotal phase 2 trial of SL 401 patients with blastic plasmacytoid dendritic cell neoplasm. *EHA learn cent.* 2018; 214438
- [23] Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. *N Engl J Med.* 2019; 380(17): 1628-1637
- [24] Montero J, Stephansky J, Cai T, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm Is Dependent on BCL2 and Sensitive to Venetoclax. *Cancer Discov.* 2017; 7(2): 156-164.
- [25] Philippe L, Ceroi A, Bôle-Richard E, et al. Bortezomib as a new therapeutic approach for blastic plasmacytoid dendritic cell neoplasm. *Haematologica.* 2017; 102(11): 1861-1868.
- [26] Ceribelli M, Hou ZE, Kelly PN, et al. A Druggable TCF4- and BRD4-Dependent Transcriptional Network Sustains Malignancy in Blastic Plasmacytoid Dendritic Cell Neoplasm. *Cancer Cell.* 2016; 30(5): 764-778.
- [27] Emadali A, Hoghoughi N, Duley S, et al. Haploinsufficiency for NR3C1, the gene encoding the glucocorticoid receptor, in blastic plasmacytoid dendritic cell neoplasms. *Blood.* 2016; 127(24): 3040-3053.

