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Commentary

Puerile and Forager-Blastic Plasmacytoid Dendritic Cell Neoplasm

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Received: February 08, 2023; **Published:** February 22, 2023

Blastic plasmacytoid dendritic cell neoplasm is an exceptional malignant haematological disorder derived from plasmacytoid dendritic cells (pDC). Non neoplastic counterpart of the malignant condition is configured from plasmacytoid dendritic cells.

Blastic plasmacytoid dendritic cell neoplasm is additionally designated as blastic natural killer (NK) lymphoma, agranular CD4+/ CD56+ hematodermic neoplasm, agranular CD4+ NK cell leukaemia or CD56+ TdT+ blastic NK cell lymphoma.

Demonstrating an aggressive clinical course, majority (80%) of subjects manifest cutaneous lesions along with neoplastic occurrence confined to bone marrow or lymph nodes. Blastic plasmacytoid dendritic cell neoplasm incriminating paediatric subjects may represent with mild clinical course.

Neoplastic cells appear immune reactive to CD123, TCF4, CD4, CD56 and TCL1. Cogent segregation of blastic plasmacytoid dendritic cell neoplasm from acute myeloid leukaemia (AML) is necessitated, especially for commencement of appropriate therapy.

Blastic plasmacytoid dendritic cell neoplasm exhibits a male predominance with male to female proportion of ~3:1 [1,2].

The neoplasm commonly emerges within fifth decade or sixth decade although no age of disease emergence is exempt.

Blastic plasmacytoid dendritic cell neoplasm commonly incriminates cutaneous surfaces, bone marrow, lymph nodes or spleen although no anatomic site of disease emergence is exempt. Around 10% instances delineate neoplastic dissemination within cerebrospinal fluid (CSF) upon initial disease representation wherein disease relapse is associated with significant neoplastic dissemination within cerebrospinal fluid [1,2].

Blastic plasmacytoid dendritic cell neoplasm is posited to arise from plasmacytoid dendritic cell(pDC) which contributes to concordance of innate and adaptive immune mechanisms. Also, mono-allelic and bi-allelic deletions within chromosome 12p or ETV6 gene represents as a preliminary pathogenic event [1,2].

Transcriptional network specific to blastic plasmacytoid dendritic cell neoplasm is regulated with E-box transcription factor TCF4 (E2-2). The molecule predominantly contributes to regulation of neoplastic cells and appears to be controlled by bromodomain and extra-terminal domain (BET) protein BRD4. Epigenetic dysregulation frequently ensues due to genetic mutations occurring within DNA methylation, histone methylation and chromatin remodelling [1,2].

NR3C1 haplo-insufficiency is frequently concurrent to aberrant overexpression of contemporary long noncoding RNA (lnc RNA) gene, lincRNA-3q. Products of aforesaid genes appear incriminated within G1/S phase of cellular cycle transition through concurrence of E2F. Survival of neoplastic cells configuring blastic plasmacytoid dendritic cell neoplasm is primarily dependent upon BCL2.

Besides, neoplastic cells demonstrate features of non activation state and emerge in concurrence with immunodeficiency [1,2].

Of obscure aetiology, blastic plasmacytoid dendritic cell neoplasm is frequently associated with diverse myeloid malignant disorders as chronic myelomonocytic leukaemia or myelodysplastic syndrome.

A specific bacterial or viral pathogen remains unidentified [1,2]. Cutaneous lesions of blastic plasmacytoid dendritic cell neoplasm appear heterogeneous as bruise-like, violaceous, maculopapular lesions, nodules, plaques or exanthema. Around ~ 10% subjects demonstrate an overt representation of leukaemia. B symptoms as pyrexia, night sweats and > 10% loss of body weight may ensue. Besides, lymph node enlargement and splenomegaly may be encountered [2,3].

Upon microscopy, bone marrow biopsy exhibits diffuse infiltration with neoplastic plasmacytoid dendritic cells which appear to replace normal hematopoietic elements. Neoplastic cells may be blastoid or pleomorphic [2,3].

With Wright-Giemsa staining, neoplastic cells appear elongated, mildly tapered cells demonstrating a tail and imbued with slightly basophilic, a-granular cytoplasm, blastoid nucleus, open nuclear chromatin and prominent nucleolus. Occasionally, neoplastic cells demonstrate cytoplasmic microvacuoles arranged along cytosolic segment of cellular membrane.

Characteristically, cutaneous infiltration of immature, blastoid neoplastic cells within superficial and deep seated dermis is frequently associated with expansion into subjacent subcutaneous tissue. Typically, incrimination of superimposed epidermis is absent. Mitotic activity is significant [2,3].

Benign	Malignant
Tuberculosis	Acute myeloid leukaemia
Toxoplasmosis	Leukaemia cutis
Sarcoidosis	Myeloid sarcoma
Histiocytic necrotizing lymphadenitis	Extra-nodal NK/T cell lymphoma, nasal type
Castleman disease	Cutaneous T cell lymphoblastic leukaemia/lymphoma
Systemic lupus erythematosus	Primary cutaneous T cell lymphoma
Lichen planus	
Psoriasis	
Contact dermatitis	

Table 1: *Differential diagnosis of blastic plasmacytoid dendritic cell neoplasm [3,4].*

Blastic plasmacytoid dendritic cell neoplasm is immune reactive to TCF4, CD123, CD4, CD56, TCL1, CD43, CD45, BCL2, CD2AP, and HLA-DR. The lymphoma is variably immune reactive to CD2, CD5, CD7, CD10, CD33, CD38, CD68, CD117, BCL6, terminal deoxynucleotidyl transferase (TdT) and S100 protein. Nevertheless, CD2, CD3, CD13, CD5, CD10, CD38, CD117, MUM1/IRF4, BCL2, BCL6 or S100 protein are occasionally immune reactive. Few neoplasms appear immune reactive to PD1.

Besides, the lymphoma appears immune reactive to CD43, CD45RA, CD36, CD303/BDCA2, CD304/BDCA-4, ILT3, CD2AP, TCL1or SPI-B. Frequent, *de novo* immune reactivity to CD56, CD7, CD33 and terminal deoxynucleotidyl transferase (TdT) is observed. Ki67 proliferation index is elevated [4,5].

Blastic plasmacytoid dendritic cell neoplasm is immune non reactive to lineage specific markers as CD3, CD19, CD20, CD34, PAX5, lysozyme, myeloperoxidase, myeloid cell nuclear differentiation antigen (MNDA), CD68, cutaneous lymphocyte associated antigen (CLA)/ CD162 or granzyme B [4,5].

Flow cytometry can be adopted to segregate blastic plasmacytoid dendritic cell neoplasm from variants of acute leukaemia, preponderantly acute myeloid leukaemia (AML). Cogent discernment of proliferating mature plasmacytoid dendritic cells(pDC) concordant to exclusion of myeloid neoplasms, primarily chronic myelomonocytic leukemia and measurable or minimal residual disease (MRD) may thus be ascertained [4,5].

Upon flow cytometry, neoplastic cells configure as blast gate cells immune reactive to CD45 with a side scatter (SSC).

Minimal residual disease requires appropriate distinction within neoplastic cells configuring blastic plasmacytoid dendritic cell neoplasm and non neoplastic plasmacytoid dendritic cells (pDCs) [4,5].

Cytogenetic analysis frequently demonstrates a complex cellular karyotype. Several adults exhibit genetic mutational profile and chromosomal anomalies akin to myelodysplastic syndrome.

Genomic rearrangements within ETV6 or MYC genes may be frequently encountered. Structural chromosomal losses within 13q14 (RB1), 9p21.3 (CDKN2A/CDKN2B), 12p13.2-p13.1 (CDKN1B, ETV6) or 7p12.2 (IKZF1) are commonly delineated.

Commonly, genetic mutations within TET2, ASXL1, IDH1, IDH2, DNMT3A, EZH2, SF3B1, SRSF2, ZRSR2, FLT3, KIT, KRAS or NRAS are exemplified [4,5].

Blastic plasmacytoid dendritic cell neoplasm requires segregation from malignancies such as acute myeloid leukaemia, myeloid sarcoma, mature plasmacytoid dendritic cell proliferation, B lymphoblastic lymphoma, T lymphoblastic lymphoma or neuroendocrine tumour as Merkel cell carcinoma [4,5].

For appropriate disease discernment, malignant infiltrate of blastoid cells requires segregation from proliferating mature plasmacytoid dendritic cells(pDC).

Flow cytometry or cogent immunohistochemistry can be beneficially adopted to categorize immuno-phenotype of mature plasmacytoid dendritic cells(pDC) [4,5].

Generally, cellular cytogenetic analysis or molecular evaluation appears superfluous for precise diagnosis of the neoplasm. Monolineage or bi-lineage cytopenia or pancytopenia is commonly discerned. Nevertheless, few instances demonstrate normal haematological parameters [4,5].

Upon computerized tomography (CT), pulmonary parenchyma demonstrates interstitial opacities with a ground glass configuration admixed with reticular opacities. Lymphadenopathy and hepatosplenomegaly may be enunciated [4,5].

^{18}F-flourodeoxy glucose positron emission tomography (^{18}F-FDG PET) exemplifies hypermetabolic cutaneous lesions and regional or distant lymph node metastasis. However, incrimination of bone marrow may be indiscernible upon ^{18}F-FDG PET scan.

Chemotherapy is a recommended, preferred mode of treating blastic plasmacytoid dendritic cell neoplasm in concurrence with allogeneic stem cell transplantation [4,5].

Blastic plasmacytoid dendritic cell neoplasm can be appropriately treated with tagraxofusp which represents as a CD123 targeted immunotoxin. Adoption of induction chemotherapeutic regimen applicable to acute lymphatic leukaemia (ALL) exhibits superior therapeutic outcomes, in contrast to adopted regimen of acute myeloid leukaemia (AML) [4,5].

Additionally, allogeneic stem cell transplant is recommended for healthy subjects achieving initial complete remission.

Prognostic factors contributed to with cogent pathological or molecular features remain undefined. Nevertheless, factors such as advanced disease stage or incrimination of elderly subjects are associated with inferior prognostic outcomes. Besides, the neoplasm demonstrates median survival between 12 months to 14 months [4,5].

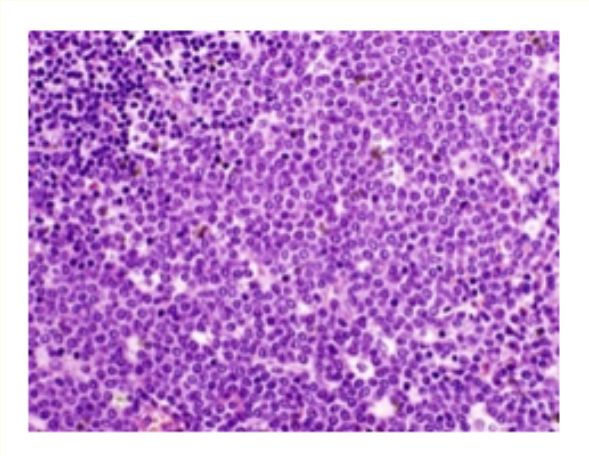

Figure 1: *Blastic plasmacytoid dendritic cell neoplasm comprised of blastic, pleomorphic cells imbued with scanty basophilic cytoplasm, enlarged nuclei with open nuclear chromatin and prominent nucleolus [6].*

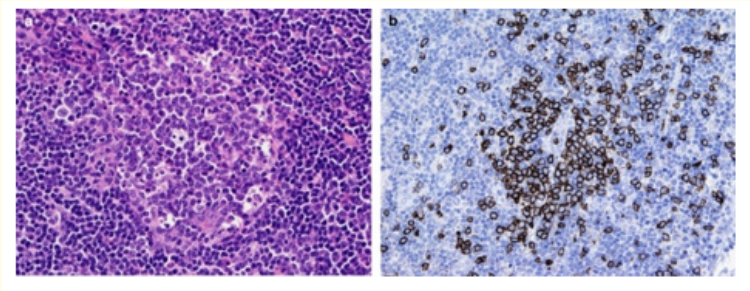

Figure 2: *Blastic plasmacytoid dendritic cell neoplasm exhibiting pleomorphic cells incorporated with scanty cytoplasm, enlarged nuclei, vesicular chromatin and prominent nucleoli. Neoplastic cells appear immune reactive to CD303 [7].*

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6. Image 1 Courtesy: Science direct.

7. Image 2 Courtesy: Nature.

Volume 22 Issue 3 March 2023