Abstract:
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare form of haematologic neoplasm with aggressive clinical behaviour and is characterized by its typical immunophenotype and clinical presentation. There have been many case reports in the recent past and this entity has been renamed in the recent WHO classification of tumours (2008). We report a case of a 53 yr old male, who presented with skin lesions since 8 months and misdiagnosed outside as cutaneous lymphoma and acute myeloid leukemia, for which he underwent chemo-radiotherapy and had been referred to our institution for further management. On histopathological evaluation he was diagnosed to have BPDCN, this was also confirmed by flow cytometry. This case is reported for its rarity and potential for misdiagnosis.

Keyword: Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

A 53 year old gentleman presented with an eight month history of diffuse skin lesions; varyingly diagnosed in two different hospitals as cutaneous lymphoma and acute myeloid leukemia. He had received one cycle of chemotherapy substituted with whole body irradiation for 9 weeks due to intolerance to chemotherapy. Subsequent to treatment initiation his peripheral blood smear revealed presence of blasts, and was referred to our centre for further management on additional 6-mercaptopurine. He had significant loss of weight and appetite since 6 months. Additionally the patient was a known diabetic on insulin for sugar control. On general examination, he was pale with generalized lymphadenopathy. Multiple generalized erythematous, non-tender, plaques, papules and nodules were noted. There were lesions with erosions with desquamation in the abdominal wall. Tenderness and induration was present in left forearm and thigh over an area of approximately 8x6cm. Swelling over right parotid region was noted. Bilateral pitting paedal oedema was present. There was no organomegaly. Baseline laboratory investigations revealed the following; Haemoglobin – 6.5g%; total WBC count – 900/cumm; differential count (on 5 cells) – neu-
Cytogenetic analysis revealed a normal karyotype. Skin biopsies from chest wall and abdominal wall showed pan dermal diffuse, nodular, infiltrate of medium sized cells with round to oval nuclei, clumped chromatin, indented nuclear membranes and moderate amounts of pale eosinophilic cytoplasm, exhibiting increased mitotic activity. [Fig. 3]. The infiltrate were also seen in the periadnexal, perivascular and perineural region. The infiltrate was also seen to stream between the collagen bundles and extend into the lobules of the subcutaneous fat. Occasional atypical cells were seen extend into the dermo-epidermal junction. There were no foci of necrosis.

<table>
<thead>
<tr>
<th>Bone marrow</th>
<th>Positive</th>
<th>Negative</th>
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<tbody>
<tr>
<td>Immuno-chemistry</td>
<td>CD4, CD56, CD123 and PGM1</td>
<td>CD3, CD20, CD8, Tdt, CD34 and MPO</td>
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**Figure 3: BPDCN – Skin biopsy showing pandermal diffuse infiltrate of the neoplastic cells (H&E 400x)**

On immunohistochemistry: These medium sized cells were positive for CD4, CD56 and CD123 with a MIB-1 labeling index of 70%. They were negative for CD3, CD20, MPO and CD30.
Many cells showed cytoplasmic dot like positivity for CD68. A diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN) was made.

Discussion:
BPDCN is a rare aggressive neoplasm derived from a clonal population of precursor plasmacytoid dendritic cells, also called as type I interferon producing cells (1). It accounts for less than 1% of all acute leukemias (2). Most of the patients are elderly (61-67 yrs) with a definite predilection towards male sex (M: F – 3.3:1). It can occur in childhood as well (1).

Site of involvement:
Skin involvement is seen in all cases (100%), followed by bone marrow and peripheral blood (60-90%) and lymph node (40-50%) (1). Paediatric cases tend to have less frequent cutaneous involvement (3). Multiple organs that can be involved on relapse and progression of the disease include central nervous system, spleen, soft tissue, nasopharynx, gums and bronchial mucosa (1,2).

Clinical features: Usual presentation (in 90% of the patients) is an indolent course with a solitary or multiple skin lesions such as plaques, nodules or bruise like areas (1,4). However 10% can present with features of acute leukemia with systemic involvement (4). This acute leukemic variant can have increased leukocyte count, presence of blasts in the peripheral blood, massive bone marrow infiltration and multiple skin nodules (2) as like in our patient. Cytopenias at presentation indicates bone marrow failure (1). Although initial response to chemotherapy is good with a high remission rate, most patients eventually develop progressive disease or relapse with most of them ultimately developing a fulminant leukemic phase (1,2,5). Unlike the leukaemic variant, some (10-20%) of the patients are associated with or develop secondary acute myeloid leukaemia or chronic myelomonocytic leukaemia which are phenotypically different from BPDCN (2).

Aetiology: There is no definitive aetiology has been reported till date. There is no association with Epstein Barr Virus (1,2).

Histogenesis: BPDCN arises from the precursor of the type I (alpha) interferon producing plasmacytoid dendritic cells (1). The mature forms are normally found in T-cell zones of lymph nodes and tonsils and rarely in thymus and other lymphoid tissues (2,5). They have the capability to differentiate into an antigen presenting cell upon appropriate stimuli. The typical location in the lymph node is near the high endothelial venules. They are medium sized cells with a single round to oval or indented nucleus, finely dispersed chromatin and 1-2 small nucleoli and moderate amounts of eosinophilic cytoplasm. Immunophenotype of these cells are CD68, BDCA2, CD123, CD2AP, TCL1 and BCL11a. There is an increase in the number of these cells in certain disease conditions including Kikuchi disease, hyaline vascular variant of Castleman disease, granulomatous inflammation, myeloproliferative disorders and in lymph nodes with metastatic tumour (2,5). It has a vital role in certain autoimmune diseases such as systemic lupus erythematosus and psoriasis by producing interferon, where it accumulates in the tissue rather than in the peripheral blood. It strongly suppresses the HIV infection of CD4+ T-lymphocytes and hence is reduced in the HIV patients with severe viral load corresponding to the decrease in CD4 cell count (2).
**Histology:**

Bone marrow may show a subtle interstitial infiltrate or a focally dense or diffuse monotonous infiltrate of medium sized blast cells with irregular nuclei, fine chromatin and 1 to several small nucleoli and scant agranular cytoplasm. Dysplastic megakaryocytes are usually seen. Angioinvasion and coagulative necrosis are usually absent (1,2). Skin shows predominantly dermal infiltrates, extending into subcutaneous fat (1). Epidermotropism is not seen and usually has a clear grenz zone between the tumour and the epidermis except for rare cases (7). Unusual histological features in cutaneous lesions observed in a study include, perianadrnexal pattern, angiocentricity without angio destruction, several reactive lymphoid follicles with germinal centres within the tumour and pleomorphism with elongated/twisted/hyperchromatic cells. This unusual histology can lead to misdiagnosis (7). Lymph nodes show leukaemic pattern of infiltration involving interfollicular and medullary region (1). FNA smears from lymph nodes stained with nuclear stains show medium sized cells with blastic features or may resemble mature lymphoid cells (mantle zone) or atypical monocytes (2). Bone marrow and peripheral blood smear show cytoplasmic microvacuoles along the cell membrane and pseudopodia (2).

**Cytochemistry:** BPDCN tumour cells are non reactive for -naphthyl acetate/butyrate esterase (NSE), naphthol AS-D chloroacetate esterase (CAE) and myeloperoxidase (MPO) (2). **Immunohistochemistry:** The tumour cells are usually positive for specific plasmacytoid dendritic cell markers such as CD123, BDCA-2 (CD303), TCL-1, CD2AP and BCL11a (2). CD123, an IL3 receptor- subunit protein, has a fundamental role in PDC survival and function. BDCA-2 (CD303) is a C-type lectin transmembrane glycoprotein/blood dendritic cell antigen-2, which is involved in antigen uptake and regulation of interferon production by PDCs. This is currently considered as the most specific marker for these cells and its expression depends upon the tumour cell differentiation/activation. CD68, a histiocytic/dendritic cell marker shows cytoplasmic dot like positivity in 50% of the cases and Tdt is positive in one-third of the cases. Tdt (Terminal deoxynucleotidyl transferase) expression is inversely proportional to BDCA-2 expression as explained by the spectrum of maturation, that BDCA-2 is expressed in more mature tumour cells and Tdt in more immature ones (7,8). Whereas a positive correlation is obtained between the expression of BDCA-2 and CD7 and BDCA-2 immunoactivity indicates aggressiveness and herald a significant decrease in survival (8). Markers for myeloid precursors such as CD34 and CD117 are usually negative (2). Other markers expressed by these tumour cells are CD4, CD56, CD101, BDCA-4, IRF-8 and BCL11a (7). Unusually CD4, CD56, CD123 and/or TCL-1 may be negative in the tumour cells (7). Some rare cases have shown CD34 positivity (9). Characteristic absence of EBER (EBV encoded RNA) positivity indicating no association with EBV is found (1,2).

**Flow cytometry:** Immunophenotype that is pathognomonic of BPDCN is lack of lineage associated antigens together with expression of CD4, CD45RA, CD56 and CD123 (2,4). Other immunophenotype in flow cytometry are CD36, CD38, BDCA-2 and HLA-DR. The negative markers include CD45RO, CD57, CD117, MPO and CD116 (2,4). Cytoplasmic expression of nucleophosmin (surrogate marker for NPM1 mutation) is not identified and it has a wild type gene (distinguishes BPDCN.
from myeloid leukaemia) (4,7). **Genetics:** Two-thirds of the cases show karyotypic abnormality with distinctive feature of karyotypic abnormalities (~6-8 abnormalities) in the same cell. The most common ones are 5q, 12p, 13q, 6q, monosomy 15 and 9 in the decreasing order of frequency (2). Losses are frequently detected with more frequent deletion of chromosome 9, 13 and partial loss of 17p or 12p. These various genetic events could contribute to the chemoresistance of the tumour (10). IgH or TCR gene rearrangements are mostly not seen. Rare case reports with TCR gene clonality was found and thought to be due to the strong immune response to a dominant epitope (7).

**Differential diagnosis:** Precursor lymphoblastic lymphoma/leukaemia can be distinguished by the presence of lineage specific antigen expression or gene rearrangement studies. Cutaneous NK/T cell lymphoma, nasal type can be distinguished by the cellular pleomorphism and its characteristic feature of angioinvasion and necrosis and immunohistochemistry showing the presence of cytotoxic molecules and cytoplasmic CD3 and in situ hybridization for EBER positivity. Langerhan cell histiocytosis can be distinguished by its typical cytomorphology, background eosinophils and immunohistochemistry for CD1a, S-100 and Langerin (2).

**Prognosis:** Clinical course is very aggressive with a median survival of 12-14 months (2,4,5). Adverse prognostic factors include older age (>60 yrs), extracutaneous involvement including bone marrow and peripheral blood and high blast counts (11). Younger patients (<40 yrs) with restricted or isolated skin disease, Tdt expression seen in >50% of the tumour cells and aggressive initial treatment with acute leukaemia protocol, show a better prognosis (2,6). Paediatric cases usually have complete remission with better prognosis and long term survival (3). In a study done on variations in cutaneous lesions, one patient with solitary skin lesion survived for 29 months with local radiotherapy alone (7). Myeloablative (aggressive) chemotherapy and/or radiotherapy followed by allogenic bone marrow transplant is the best treatment modality reported with increased chance of long term survival in the younger patients who are eligible for bone marrow transplant (3,4,6,11). Routine CSF analysis and prophylactic intrathecal chemotherapy is recommended in these patients as there is a high chance of CNS relapse (6).

**Bibliography:**


