World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

A case report on BPDCN: Blastic Plasmacytoid Dendritic Cell Neoplasm

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World Journal of Advanced Research and Reviews, 2023, 19(02), 091–098

Publication history: Received on 12 June 2023; revised on 26 July 2023; accepted on 28 July 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.19.2.1469

Abstract

Dendritic cells are present in both lymphoid and non-lymphoid organs, which are heterogenous group of nonphagocytic and nonlymphoid immune accessory cells. Plasmacytoid dendritic cell (which has an eccentric nuclei) are subset of dendritic cells aid in secreting high levels of type 1 interferons by activation and gaining dendritic cell like morphology, play an important role in antiviral immunity and are involved in initiation and development stages of inflammatory response. The initial presentation of extra-cutaneous region is an involvement of regional lymph nodes later progressed to bone marrow and peripheral blood. When bone marrow is extensively involved, neoplastic cells interfere peripheral blood resembling as circulating leukemic myeloid or lymphoid blasts. BPDCN is confused with cutaneous peripheral T-cell lymphoma due to cutaneous involvement. Comparative to adults, BPDCN in children are less aggressive. Intensive 1st line therapy along with "Lymphoid type" chemotherapy show better results. Lymphodenopathy, splenomegaly, bone marrow involvement and cytopenia, cutaneous lesions are observed widely.

Keywords: Plasmacytoid dendritic cells (pDCs); Acute myeloid leukemia (AML); Flow cytometry; Chemotherapy; Mutation; Bone marrow

1. Case description

A 46 year old male, non-diabetic, hypertensive patient with "A" positive blood group, negative for serology presented with complaints of fever (intermittent) since a month and loss of weight. The following examinations were performed over a period of time which aid in differential diagnosis and clinical intervention.

24.01.2022 – **peripheral smear study* shows marked leukocytosis and reduced platelets, the cellular elements are predominantly composed of blasts (onomorphic with increased nucleocytoplasm ratio and prominent nucleolus)

01.02.2022 – **peripheral smear study* with an impression of acute leukemia with marked thrombocytopenia and leukocytosis with prominence of **90% blasts** which are 2-3 times the size of small mature lymphocyte with prominent nucleoli and scant cytoplasm (with fine granules).

Flow cytometry panel* with an impression of myeloid neoplasm favoring blastic plasmacytoid dendritic cell neoplasm; marked leukocytosis with blast prominence of **92%.

**Flow cytometric immunophenotyping* results in gated population (s) approx. 86.98% in progenitor region with an expression of dim positive CD45, CD117 (myeloid antigen), partial dim positive CD11c (myeloid antigen) and CD4 (T lmphocytic antigens), moderate positive CD33 (myeloid antigen) and CD123 (B lymphocytic antigens), negative for CD34,CD38,HLA-DR,CD2,CD5,CD7,CD56, cytoplasmic CD3,CD14, CD15, CD64, CD36 and MPO (myeloperoxidase).

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*_Bone marrow biopsy_ examination has confirmed myeloid neoplasm favoring "blastic plasmacytoid dendritic cell neoplasm", showing bone marrow with a cellularity approx. 90% and intertrabecular spaces show diffuse sheets of blasts.

*_2D ECHO_: LVEF – 66% with an impression of good biventricular function and grade 1 diastolic dysfunction.

02.02.2022 -- *Galactomannan-Aspergillus antigen*: 2.50 index (Ref range: <0.5 (negative) and >0.5 (positive) index) suggesting infection.

18.02.2022 -- *HRCT (thorax)*: Multiple nodules (largest 1.3*1.2cm) with ill-defined margins in B/L lungs (infective/inflammatory etiology: fungal etiology), areas of consolidation in left middle lobe with air bronchogram)

*All lab investigations were assessed in NABL accredited laboratories on regular basis demonstrate constant abnormalities (Figure 1-5).

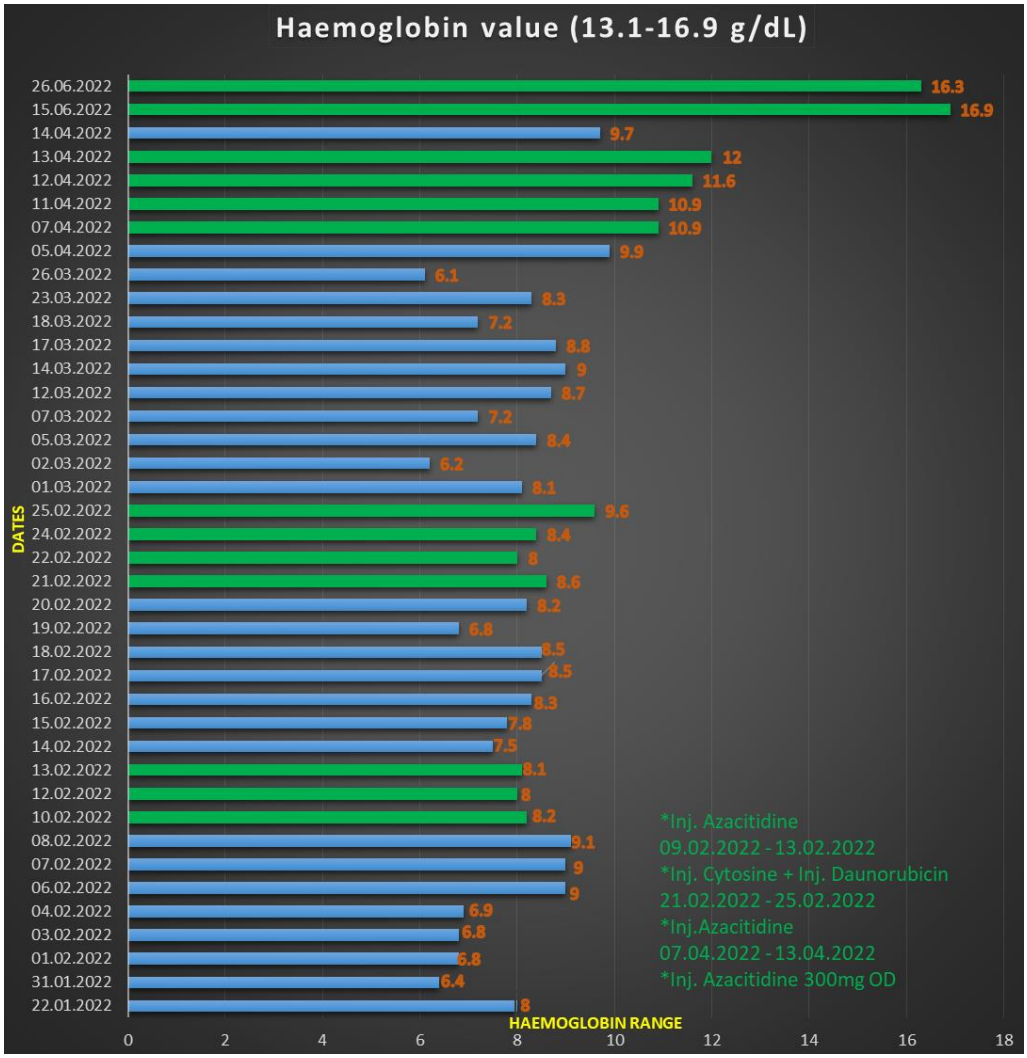

Figure 1 Abnormality in *haemoglobin values* in respective date's pre-during-post chemotherapy and transfusions

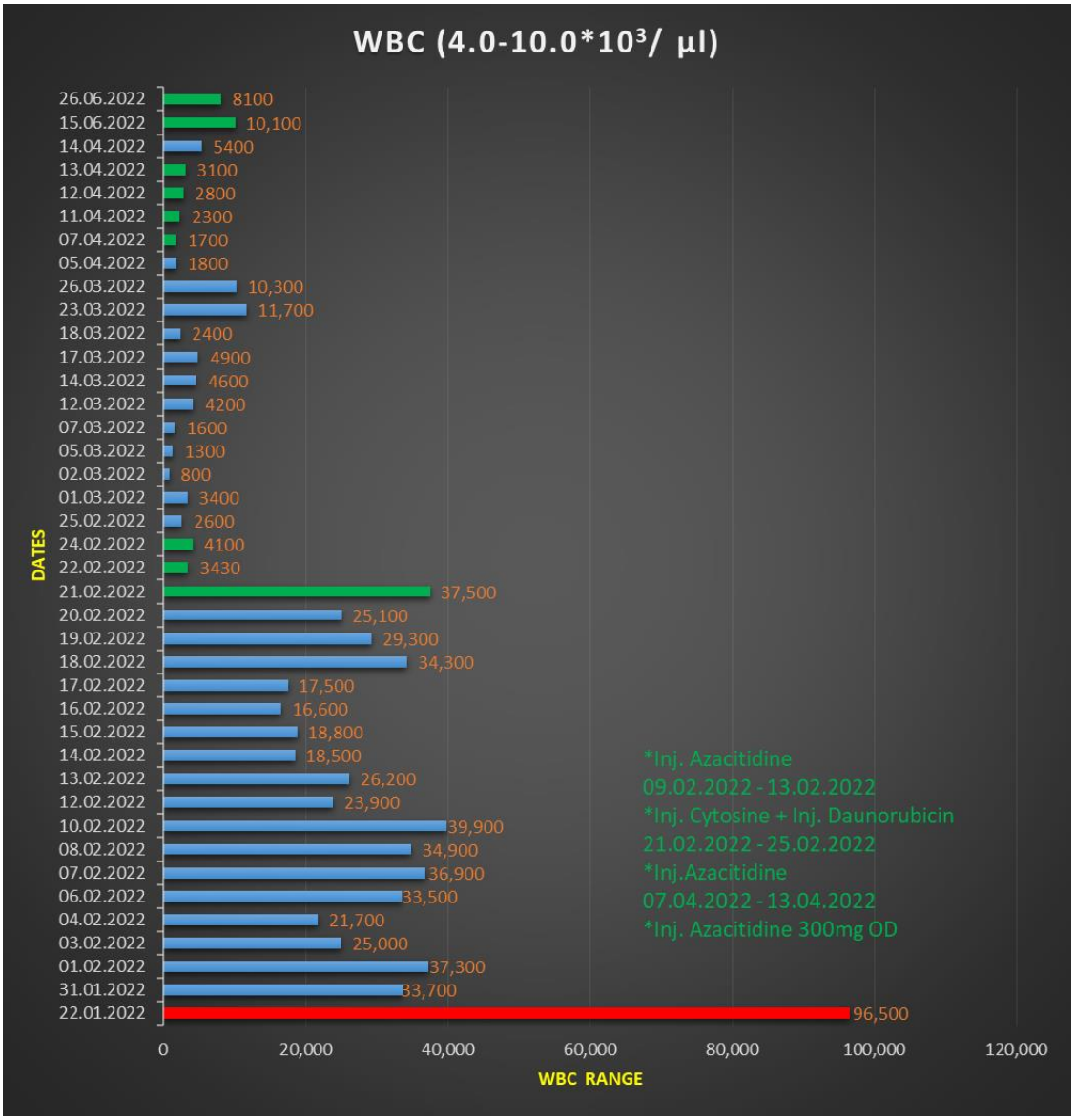

Figure 2 Abnormality in *WBC count* in respective date's pre-during-post chemotherapy and transfusion

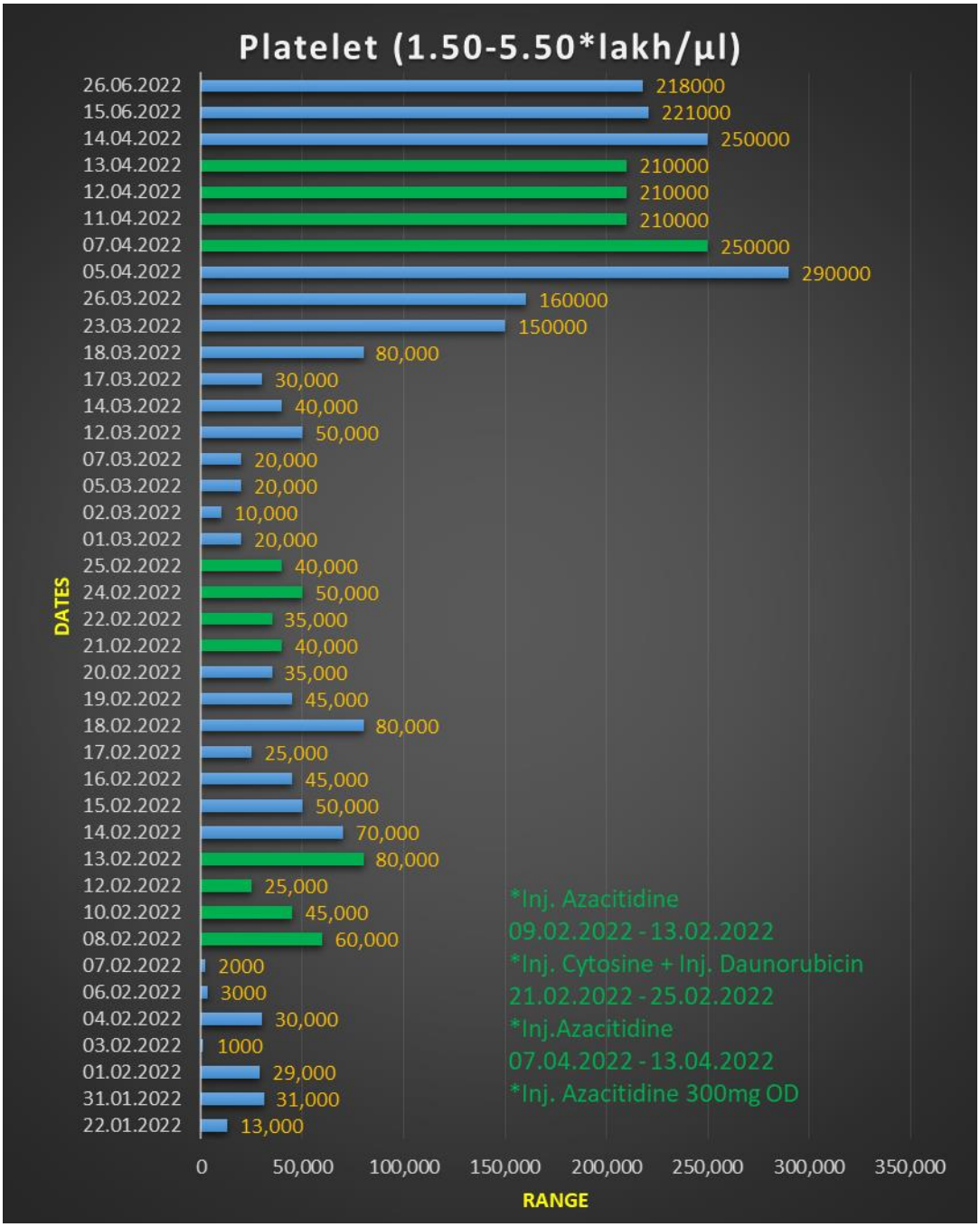

Figure 3 Abnormality in *Platelet count* in respective date's pre-during-post chemotherapy and transfusion

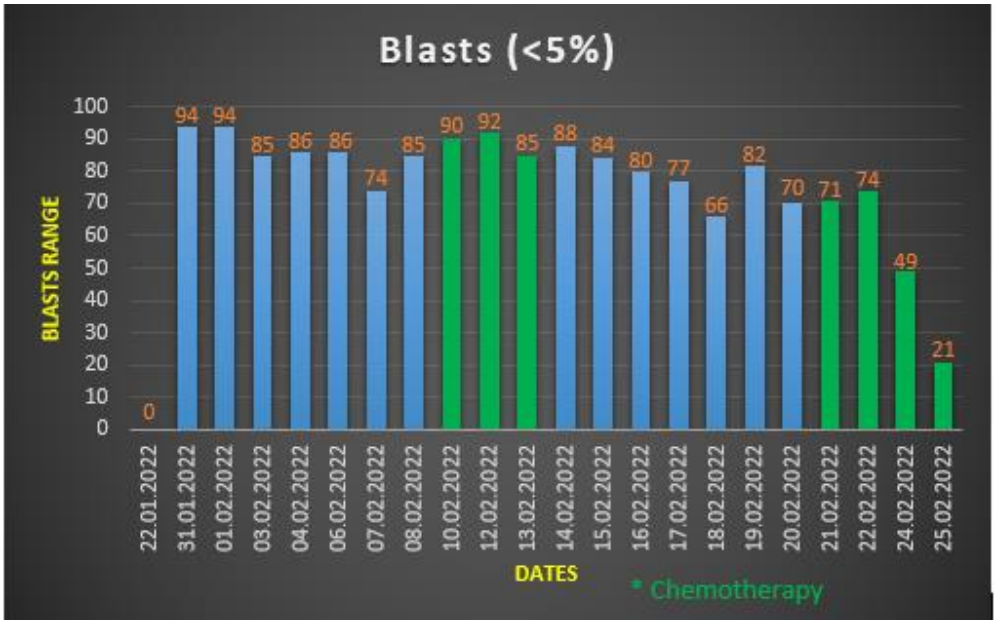

Figure 4 Abnormality in *Blast count.*

Figure 5 Abnormality in *Galactomannan-Aspergillus antigen* indicating infection.

Table 1 Abnormality in *metamyelocytes* and *band forms*

Metamyelocytes along with myelocytes and promyelocytes are precursors to neutrophils.			**Bands are immature neutrophils present in circulating blood, clinically indicates sepsis.**
	(<0.5%)	**(<1%)**	**(3-5% of WBC)**
12.03.2022	Myelocytes – 05	Metamyelocytes – 07	Band forms -06
13.03.2022	Myelocytes – 06	Metamyelocytes – 08	Band forms - 08
17.03.2022	Myelocytes – 03	Metamyelocytes - 06	Band forms -12

Table 2 Patient's transfusion historyDuring hospitalization (chemotherapy)

05.02.2022	PRBC (packed red blood cells)	Transfusion
07.02.2022	PC (packed cells)	
27.02.2022	PC	
02.03.2022	PRBC	
03.03.2022	PRBC	
04.03.2022	PC	
05.03.2022	PC	
06.03.2022	RDP (random donor platelet)	
09.03.2022	PC	
24.03.2022	PRBC	

Tab. Forcan 150mg OD, Tab. Acivir 400mg BD, Tab. Septran DS BD (twice in a week), Tab.Udiliv 300mg TID, Tab. Metxl 12.5mg OD, Inj. GCSF 30mcg S/C OD (post chemotherapy), Inj. Meropenem 1gm IV OD, Inj. Targocid 400mg IV OD, Inj. Clarithromycin 500mg BD, Inj. Pantoprazole 40mg IV OD, Inj. Magnex 3gm IV OD, Inj. MVI 1amp IV, Inj. Posaconazole 300mg IV OD 14 days, Tab. Sorbitrate 5mg S/L SOS were prescribed to treat infection and HTN (hypertension) respectively.

Table 3 1st line of induction chemotherapy

Chemotherapy (BSA 1.5 m^2)	**09.02.2022**	**10.02.2022**	**11.02.2022**	**12.02.2022**	**13.02.2022**
Inj. AZACITIDINE 75mg/m^2 100mg in 100ml NS IV over 1hr	✓	✓	✓	✓	✓

Table 4 2nd line of induction chemotherapy

Chemotherapy (BSA 1.5 m^2)	**21.02.2022**	**22.02.2022**	**23.02.2022**	**24.02.2022**	**25.02.2022**
Inj. CYTOSINE 150mcg S/C	✓	✓	✓	✓	✓
Inj. DAUNORUBICIN 50mg in 100ml NS over 1hr (dose reduced from 90mg to 50mg)				✓	✓

Patient is not in complete remission (CR) post 5+2 chemotherapy hence, patient and family were explained about treatment options i.e. Allogenic HSCT and Auto HSCT (when on CR), but as patient's family did not opt for either of option therefore consultant (hemato-oncologist) proceeded with consolidation chemotherapy and when on CR (proceed for Auto HSCT). As the condition is rare and with sparse data therefore consultant proceed with Azacitidine *vs* Methotrexate + L-Asparaginase injection. Central line inserted on 25.02.2022 (post 5+2 induction chemotherapy).

Table 5 1st line of consolidation chemotherapy

Chemo (BSA 1.46 m^2)	**07.04.22**	**08.04.22**	**09.04.22**	**10.04.22**	**11.04.22**	**12.04.22**	**13.04.22**
Inj. AZACITIDINE 75mg/m^2 in 100 ml NS IV over 1hr OD	100mg						166mg
	✓	✓	✓	✓	✓	✓	✓

1.2. Maintenance therapy

Since patient has gradually shown encouraging results Tab. Azacitidine 300mg OD from 23.06.2022 (14 days each cycle).

2.1. Introduction

Cancer is monoclonal in origin where in the division and mutation inferred from a single cell. A dendritic cell is a type of antigen presenting cell (APC) which boosts immune responses by highlighting antigens on the surface to other immune cells. WHO classifies dendritic cell neoplasms in 5 groups: Langerhans' cell sarcoma, dendritic cell sarcoma, interdigitating dendritic cell sarcoma/tumor, Langerhans' cell histiocytosis, follicular dendritic cell sarcoma/tumor [1]. Dendritic cells are present in both lymphoid and non-lymphoid organs, which are heterogenous group of nonphagocytic and nonlymphoid immune accessory cells. Follicular dendritic cells (FDC) by presenting and retaining antigens for B cells participate in immune system, also by stimulating B cell proliferation and differentiation. The cell membrane is indistinct with eosinophilic cytoplasm which tend to form clusters with lymphocytes, interaction with other cells produce a distinct appearance as giant cell. Interdigitating dendritic cell (IDC) are a type of APC which are characterized by cluster of interdigitating cellular junctions. They function antigens as peptide fragments which bind to MHC (major histocompatibility complex), the complex is recognized by the antigen receptors present on T-cell lymphocyte. IDC capture antigens on surface, transfer them to T cells (lymphatic system and spleen) from non-lymphoid organs [2].

2.2. Blastic plasmacytoid dendritic cell neoplasm

BPDCN is sub type in acute myeloid leukemia (AML) as per 2008 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue [3], rare in its form aggressive hematopoietic malignancy which is believed to be derived from precursors of pDC; earlier it was believed that the origin is from natural killer cells, monocytes however in the recent times it is understood that the distortion arise from plasmacytoid dentritic cell (pDC). Plasmacytoid dendritic cell (which has eccentric nuclei) are a subset of dendritic cells which aid in secreting high levels of type 1 interferons by activation and gaining dendritic cell like morphology, play an important role in antiviral immunity and involved in initiation and development stages of inflammatory response. pDCs are generated in bone marrow from haematopoietic stem cell through myeloid and lymphoid precursors. Earlier pDCs are referred as plasmacytoid monocytes or plasmacytoid T-cells [4]. The distribution ratio in male: female is 3:1 with a survival rate of 12 – 14 months. The tumor is identified by a decent frequency of cutaneous lesions in the initial stage followed by extra cutaneous involvement of lymph nodes, bone marrow and peripheral blood. The initial presentation of extra cutaneous region is often an involvement of regional lymph nodes later progressed to bone marrow and peripheral blood. At the time of diagnosis, mild to moderate peripheral cytopenias are common, with time and progression at the terminal stage of disease patient develop fulminant leukemia. In initial stages (cutaneous lesions) BPDCN infiltrates the dermis and on progression it extends to subcutaneous region. In the advanced stage, extensive bone marrow replacement is observed whereas in initial stage, bone marrow involvement is focal with interstitial infiltration of tumor cells. When bone marrow is extensively involved, neoplastic cells interfere peripheral blood resembling as circulating leukemic myeloid or lymphoid blasts. BPDCN cells are frequently involved in recurrent combination of deletions in tumor suppressor genes such as Tp53 (tumor protein 53), CDKN1B, RBI; mutations in TET-2 gene (Ten-eleven translocation-2) which is located on band 4q24. Cell cycle disruption at the G1/S transition contribute to pathogenesis of BPDCN.

Some studies demonstrate by IHC (immunohistochemistry) that BPDCN cells express (cluster differentiation) CD4, CD56, CD123 (interleukin-3 α-chain receptor), pDC-associated antigens, T-cell associated antigens, TdT (terminal deoxynucleotide transferase; a precursor to lymphoid cells), CD38, HLA-DR (isotype namely Human Leukocyte Antigen – DR). Flow cytometery in the diagnosis of BPDCN is advantageous both qualitative and quantitative. Expression of CD123 seen on hematopoietic precursors, usually higher and homogenous. BPDCN can be diagnosed in initial stage by flow cytometery whereas IHC can detect BPDCN in initial stage per se CLA (Cutaneous lymphocyte associated antigen) highly expressed in skin lesion. Predominance of genomic loss can be observed by cytogenic studies; karyotypic analysis demonstrates insufficiencies seen in AML or myelodysplastic syndrome. Array based comparative genomic hybridization show that chromosomal loss (complete or partial) are more than gain which is due to deletion of many regions. In the progressed stage i.e. when BPDCN is extensively involved in bone marrow, it is quite difficult to differentiate between AML and BPDCN which is due to close resemblance of leukemia-type infiltration and blastic morphology in bone marrow however, flow cytometric immunophenotyping is recommended as definitive diagnosis.

Complete response with initial chemotherepay is in between 47% and 86%. Suggestible chemotherapy would be either hyper-CVAD (combination of course A and B i.e. cyclophosphamide, vincristine, doxorubicin and Mtx, cytarabine respectively in alternation way) or CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) [5,6].

3. Conclusion

BPDCN is a rare malignancy of pDC, which was previously diagnosed as hematodermic neoplasm or blastic NK-cell lymphoma. Myeloablative conditioning (MAC) and Allogeneic hematopoietic stem cell transplantation (allo-HSCT) are showing boosting results. High dose chemotherapy followed by auto-HSC (autologous hematopoietic stem cell transplantation) or RIC (reduced intensity conditioning) allo-HSCT are also showing benefits but to a lesser extent.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest with either parties.

Statement of ethical approval

The clinical data procured, analyzed and interpreted is genuine and not fabricated. Confidentiality and integrity of clinical data is stringently maintained.

Statement of informed consent

The case report is presented with verbal consent.

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