

Different Presentations and Different Treatment Options in Blastic Plasmacytoid Dendritic Cell Neoplasms: A Case Series

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ABSTRACT

Blastic plasmacytoid dendritic cell neoplasms (BPDCN) are rare, aggressive hematologic neoplasms. Awareness about this neoplasm has increased after it was defined as a clonal plasmacytoid dendritic cell disease under histiocytic/dendritic cell neoplasms in the World Health Organization 2022 classification of myeloid and Histiocytic/Dendritic Neoplasms¹. Therapies include chemotherapy or immunotherapy²⁻⁴ though stem cell transplantation (SCT) is the best consolidative approach in eligible patients⁵. Here, we present one intensive therapy-ineligible and two intensive-therapy-eligible patients with different presentations of BPDCN.

Keywords: Bendamustine; Blastic plasmacytoid dendritic cell neoplasm; Chemotherapy; Minimal residual disease; Stem cell transplantation

Case presentations

Case1:

A 38-year-old man was admitted to our clinic with left eye swelling. A biopsy of a soft tissue mass in the left maxillary sinus and nasal cavity was performed, revealing CD20⁺ high grade lymphoma. His blood cell count, albumin level, biochemistry, hepatitis B, hepatitis C and human immunodeficiency virus (HIV) serology were normal. Bone marrow aspiration and biopsy results were negative for lymphoma involvement and positron emission computed tomography (PET-CT) was consistent with stage IE lymphoma. The cyclophosphamide, doxorubicin, vincristine, and prednisolone regimen were administered for two cycles and interim PET-CT was negative for involvement. Hematopathological examination of the mass was consistent with BPDCN, with high TdT and CD56 expression. The treatment

was changed to a hyper-cyclophosphamide, doxorubicin, vincristine, and dexamethasone (CVAD) regimen with intrathecal chemoprophylaxis. The patient received high-dose BEAM (carmustine, etoposide, cytarabine, melphalan) as a preparative regimen for autologous SCT. The patient was in complete remission (CR) for six months after transplantation. The disease relapsed with CD123⁺ peripheral blood blast cells. Karyotype analysis resulted in inversion 9 abnormality. A salvage regimen (fludarabine, cytarabine, filgrastim) was started. After treatment, the bone marrow was observed to be infiltrated with CD123⁺ and CD56⁺ plasmacytoid blasts, preceding extensive skin involvement (Figure 1). Allogeneic SCT was planned with amsacrine-containing reduced-intensity conditioning. The patient died because of poor

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performance status and severe coronavirus disease-2019 infection.

Case 2:

A 38-year-old man was admitted to our clinic with left elbow mass without other skin involvement. Bone marrow aspiration revealed CD4⁺ and CD123⁺ positive blast cells and biopsy revealed CD56- and TdT-positive BPDCN with 80% Ki-67 proliferation index. PET-CT staging was consistent with stage IV disease. Complete blood count was normal during his first admission, but the patient had pancytopenia, spontaneous disseminated intravascular coagulation, and tumor lysis before pathology results were obtained. Serology results for hepatitis B, hepatitis C, and HIV were normal. The hyper-CVAD regimen was initiated with aggressive tumor lysis and coagulopathy management. After one cycle of Hyper-CVAD and high-dose methotrexate/cytarabine; the patient achieved CR. Intrathecal chemoprophylaxis was then administered. Allogeneic SCT was planned because of the leukemic clinical presentation, but the patient had no human-leukocyte antigen (HLA)-matched sibling donors. The patient received high dose BEAM as a preparative regimen for autologous SCT. After transplantation the patient has been in CR for three years.



Figure 1. Skin involvement of blastic plasmacytoid dendritic cell neoplasm

Case 3:

A 78-year-old female patient presented with a history of atrial fibrillation, hypertension, and congestive heart failure. The patient had been diagnosed with International Staging System stage II kappa light-chain multiple myeloma 17 years before. No extramedullary involvement was observed. Vincristine, adriamycin, and dexamethasone were administered for four cycles before consolidation with high-dose melphalan (200 mg/m²) and autologous SCT. CR was achieved within two years. Thalidomide (100 mg/day) treatment was administered for twelve years due to biochemical relapse. During follow-up, a 6 cm diameter purple mass was noticed in the frontal region (Figure 2).



Figure 2. Frontal mass due to blastic plasmacytoid dendritic cell neoplasm

Upon questioning, the patient detailed the mass has been progressively growing. A biopsy of the mass revealed atypical monotonous CD4-, TdT-, CD43-, Bcl-2- and TCL1-positive blastic dendritic plasmacytoid cell infiltration. The patient had normal blood cell count, albumin level, biochemistry, hepatitis B, hepatitis C and HIV serology and no bone marrow involvement was observed. PET-CT revealed increased uptake (SUV: 8.25) in the frontal lesion. Local radiation (30 Gy) was administered and the mass in the frontal region regressed completely after

radiation, with pigmentation. Six months later, the patient was admitted again with a palpable 3 cm mass in the right submandibular region and multiple brown nodular lesions on the back and chest, with normal blood cell counts. A biopsy of the brown nodular lesions and the bone marrow revealed CD123⁺ BPDCN relapse without MUM-1, CD138, kappa or lambda monoclonal staining. PET-CT staging was consistent with stage IV disease. The skin lesions regressed after two courses of bendamustine (70 mg/m², two consecutive days/28 days) and CR was sustained for seven months after completing four courses. Relapse occurred with skin lesions and 70% blast cells in the peripheral blood smear (Figure 3). Cyclophosphamide (100 mg/day) and vincristine (1 mg/m²) were infused as salvage treatment. Venetoclax monotherapy was planned because of diffuse Bcl-2 staining of the lesions; however, the patient died from sepsis on the second day of salvage treatment.

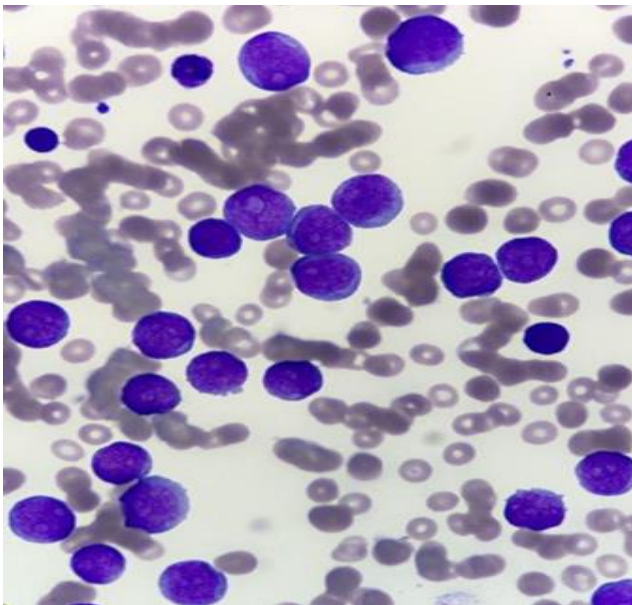


Figure 3. Blastic plasmacytoid dendritic cell neoplasm cells in the peripheral blood, 100x magnification with Giemsa stain

DISCUSSION

BPDCN is generally a neoplasm seen in older men⁶, though two of our patients discussed here were young men. Plasmacytoid dendritic cell markers (CD 123, CD 303, BDCA2, TCL1, TCF4, BCL11A, and CD2AP) are generally positive in BPDCN. Most patients (57-66%) present with complex karyotypes. Deletions of the chromosomes 9, 12p13 and 13q13 were common; patients with 6q deletions have been reported. MYC aberrations are poor prognostic factors associated with immunoblastoid variants; this may serve as a potential therapeutic target. MYB aberrations are generally seen with 6q23.3 rearrangements with unknown clinical impact^{6,7}. In the first case, inversion 9, which had no known phenotypic impact, was detected by karyotype analysis.

The first sign of BPDCN is generally skin involvement, after which pancytopenia and visceral involvement typically occur⁶. Disseminated skin involvement was observed in the relapses in the first and third cases. The morphological diagnosis of BPDCN can be challenging, as it can mimic lymphomas and monoblastic leukemia, as in our first case⁸.

Neurological involvement in BPDCN has been reported to be 30-100%⁸, and occult central nervous system involvement is possible⁶. In our patients, lumbar punctures at diagnosis and follow-up were negative for involvement, and cranial imaging findings were normal. There are no guidelines regarding appropriate central nervous system prophylaxis. Because there is insufficient evidence, intrathecal methotrexate was used as a prophylaxis to maintain safety.

The third patient had a history of MM. Approximately 10-20% of patients have a history of hematological malignancy, and the association between BPDCN and MM is rarely reported in the literature^{9,10}.

Tagraxofusp is an anti-CD123 antibody approved by the Food and Drug Administration for treating patients with untreated or relapsed/refractory BPDCN⁶. In Turkey, because tagraxofusp is not covered by health insurance companies, different chemotherapy options are preferred. Although the BPDCN showed an acute myeloid leukemia-like profile in genomic analysis, acute lymphoblastic

leukemia-like regimens showed better results for unclear reasons³. Although no prospective randomized studies have compared ALL-based chemotherapies and tagraxofusp, real-life experience suggests first-line ALL-based regimens are associated with higher response rates and comparable progression-free survival and overall survival (OS) rates to tagraxofusp¹¹.

There is an unmet treatment need for patients who are not suitable for intensive treatment or having relapsed refractory disease⁶. Azacytidine, enasidenib, venetoclax, pralatrexate have been studied in older unfit patients with BPDCN, with a possible clinical use in young, fit patients in the future⁴. A case series was published reporting patients responding to bortezomib-lenalidomide and dexamethasone treatment¹². Daratumumab was reported to be effective in two cases^{13, 14}. Betrian et al. administered bendamustine to five patients with advanced and relapsed BPDCN, one of whom responded well¹⁵. The third patient presented with bone marrow, lymph node, and skin involvement after isolated skin involvement, as well as relapse after a short period of radiation therapy. Lower-intensity agent was preferred in this patient who was not suitable for intensive chemotherapy. This case report shows that treatment with bendamustine provided a higher-than-expected average life expectancy in an older patient with BPDCN.

We performed measurable residual disease (MRD) assessments in the first two patients using 10-color flow cytometry. Both patients had a positive bone marrow MRD status ($17.6/10^{-4}$ for the first patient and $13.5/10^{-4}$ for the second). CD4 and CD123 analyses were performed for MRD assessment. Residual disease evaluation may be challenging after treatment in patients with a low tumor burden, and reactive plasmacytoid dendritic cells should be looked for¹⁶. There have been no studies on the effect of pre- and/or post-transplantation MRD status on transplantation outcomes. Additionally, there have been no studies on maintenance treatment options using novel agents for BPDCN after induction or transplantation. The loss of MRD during follow-up may guide clinicians in planning early salvage treatments.

A recent meta-analysis of 128 cases showed a pooled overall survival of 67% for allogeneic SCT in the first CR, while it was 7% for transplants beyond the first CR¹⁷. Authors reviewed the literature for the largest trials and currently recommend allogeneic SCT as a frontline consolidative treatment⁵. Concerns about the high transplantation-related mortality associated with allogeneic transplantation encouraged us to search for autologous transplantation results. Studies on autologous transplantation have been small and retrospective with most known studies showing conflicting results. A previous study demonstrated that the median OS was 6.6 years transplanted recipients (5 autologous and 20 allogeneic); however, in the entire cohort of 54 patients, the median OS was 2.0 years. Positive staining for TdT was associated with improved survival, while a normal karyotype was associated with a trend toward improved survival¹⁸. Our first patient had an abnormal karyotype but the second case had a normal karyotype; both showed TdT positivity on immunohistochemistry.

Although MRD-positive, our first two patients were in morphological remission, and as the second patient had no suitable donor, we preferred autologous transplantation due to the high transplantation-related mortality in the allogeneic transplantation.

CONFLICT OF INTEREST

The authors declare they have no financial interests.

Ethics: Written informed consents were obtained from the patients. Ethical board approval is not needed for case reports according to institutional guidelines.

REFERENCES

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 2022;36(7):1720-1748.
2. Adimora IJ, Wilson NR, Pemmaraju N. Blastic plasmacytoid dendritic cell neoplasm (BPDCN): A promising future in the era of targeted therapeutics. *Cancer*. 2022;128(16):3019-26.
3. Haddadin M, Taylor J. Chemotherapy Options for Blastic Plasmacytoid Dendritic Cell Neoplasm. *Hematol Oncol Clin North Am*. 2020;34(3):539-52.
4. Lane AA. Novel Therapies for Blastic Plasmacytoid Dendritic Cell Neoplasm. *Hematol Oncol Clin North Am*. 2020;34(3):589-600.
5. Kharfan-Dabaja MA, Cherry M. Hematopoietic Cell Transplant for Blastic Plasmacytoid Dendritic Cell Neoplasm. *Hematol Oncol Clin North Am*. 2020;34(3):621-9.
6. Zhang Y, Sokol L. Clinical Insights into the Management of Blastic Plasmacytoid Dendritic Cell Neoplasm. *Cancer Manag Res*. 2022;14:2107-17.
7. Sakamoto K, Takeuchi K. Cytogenetics of Blastic Plasmacytoid Dendritic Cell Neoplasm: Chromosomal Rearrangements and DNA Copy-Number Alterations. *Hematol Oncol Clin North Am*. 2020;34(3):523-38.
8. Deconinck E, Petrella T, Garnache Ottou F. Blastic Plasmacytoid Dendritic Cell Neoplasm: Clinical Presentation and Diagnosis. *Hematol Oncol Clin North Am*. 2020;34(3):491-500.
9. El Hussein S, Wang W, Wang SA, et al. Blastic plasmacytoid dendritic cell neoplasm with history of myeloma and concomitant acute undifferentiated leukemia: Illustration of morphologic and immunophenotypic challenges of an emerging phenomenon. *Leuk Lymphoma*. 2021;62(13):3296-3299.
10. Pemmaraju N, Kantarjian HM, Khoury JD, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Commonly Presents in the Setting of Prior or Concomitant Hematologic Malignancies (PCHM): Patient Characteristics and Outcomes in the Rapidly Evolving Modern Targeted Therapy Era. *Blood*. 2019; 134 (Supplement_1): 2723.
11. Yun S, Chan O, Kerr D, et al. Survival outcomes in blastic plasmacytoid dendritic cell neoplasm by first-line treatment and stem cell transplant. *Blood Adv*. 2020;4(14):3435-42.
12. Marmouset V, Joris M, Merlusca L, et al. The lenalidomide/bortezomib/dexamethasone regimen for the treatment of blastic plasmacytoid dendritic cell neoplasm. *Hematol Oncol*. 2019;37(4):487-489.
13. Iversen KF, Holdgaard PC, Preiss B, et al. Daratumumab for treatment of blastic plasmacytoid dendritic cell neoplasm. A single-case report. *Haematologica*. 2019;104(9):e432-e433.
14. Mirgh S, Sharma A, Folbs B, et al. Daratumumab-based therapy after prior Azacytidine-Venetoclax in an octagenarian female with BPDCN (blastic plasmacytoid dendritic cell neoplasm) - a new perspective. *Leuk Lymphoma*. 2021;62(12):3039-3042.
15. Bétrian S, Guenounou S, Luquet I, et al. Bendamustine for relapsed blastic plasmacytoid dendritic cell leukaemia. *Hematol Oncol*. 2017;35(2):252-255.
16. Wang W, Khoury JD, Miranda RN, et al. Immunophenotypic characterization of reactive and neoplastic plasmacytoid dendritic cells permits establishment of a 10-color flow cytometric panel for initial workup and residual disease evaluation of blastic plasmacytoid dendritic cell neoplasm. *Haematologica*. 2021;106(4):1047-55.
17. Kharfan-Dabaja MA, Reljic T, Murthy HS, et al. Allogeneic hematopoietic cell transplantation is an effective treatment for blastic plasmacytoid dendritic cell neoplasm in first complete remission: systematic review and meta-analysis. *Clin Lymphoma Myeloma Leuk*. 2018;18(11):703-709.e1.
18. Taylor J, Haddadin M, Upadhyay VA, et al. Multicenter analysis of outcomes in blastic plasmacytoid dendritic cell neoplasm offers a pretargeted therapy benchmark. *Blood*. 2019;134(8):678-687.