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CASE REPORT

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Blastic plasmacytoid dendritic cell neoplasm: challenges in diagnosis and treatment with potential of venetoclax as an alternative to vincristine in high-risk patients—a case report

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Abstract

Background Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and challenging cancer for diagnosis and treatment. Accurate diagnosis plays a crucial role guiding appropriate treatment, typically involving high-intensity lymphoblastic leukemia regimens which typically include vincristine. However, the use of vincristine may be particularly limited in patients with pre-existing neuropathy or individuals at high risk of developing it. Here, we present a case of BPDCN that was initially diagnosed as marginal zone lymphoma (MZL) and subsequently as non-specific T-cell lymphoma, thus highlights the importance of accurate diagnosis and modified treatment.

Case presentation A 49-year-old Arab man with a medical history of diabetes, peripheral neuropathy, hypertension, and depression presented with widespread, painless multiple skin lesions. After undergoing a biopsy at another institution, the patient was initially diagnosed with MZL, and received two cycles of bendamustine and rituximab. However, the disease relapsed and was later diagnosed with non-specific T-cell lymphoma, which proved refractory to a single cycle of CHOP chemotherapy. The patient was subsequently referred to our centre, where a comprehensive evaluation revealed BPDCN with a unique finding on bone marrow exam: signet ring plasmacytoid dendritic cells. Due to the patient's pre-existing neuropathy and previous treatment, we administered the Hyper-CVAD regimen with a 50% reduction in vincristine dosage, which resulted in an excellent response. During the second part of cycle one, when new skin lesions started appearing, venetoclax was added to the treatment regimen. Subsequently, we discontinued vincristine due to worsening neuropathic pain and neuropathy-related weakness. Venetoclax was continued in cycle two and led to a complete response. The patient achieved a disease-free state for the first time in disease course, maintaining it for a period of over six weeks before experiencing a relapse.

Conclusions Accurate diagnosis is crucial for guiding appropriate treatment. Our case highlights the challenges associated with diagnosis and treatment, as well as the potential of venetoclax as an alternative to vincristine, particularly in patients with pre-existing neuropathy or those at a high risk of developing it. Further research is needed to evaluate the effectiveness of BCL2 inhibitors as a replacement for essential drugs and its potential as a bridging therapy until patients can undergo a stem cell transplant.

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Keywords Blastic plasmacytoid dendritic cell neoplasm, Vincristine related neuropathy, Venetoclax, Hyper-CVAD, Case report

Background

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematologic malignancy that originates from type I interferon-producing cells of the immune system known as plasmacytoid dendritic cells (pDCs) (Khoury 2018). It accounts for less than 1% of all hematologic malignancies, with an estimated incidence of 0.04 cases per 100,000 individuals (Orazi et al. 2013). The disease typically affects individuals between 60–70 years, with a male-to-female ratio of 3:1 (Orazi et al. 2013; Chaperot 2001).

The clinical presentation is variable, but skin tumors with or without features of leukemia are the most common manifestation, affecting 80–90% of cases. Other commonly affected sites with these abnormal cells include lymph nodes, spleen, central nervous system, and bone marrow (Pagano et al. 2013). Skin lesions usually appear as dark purple, nodular growths that rapidly progress to large tumors without specific distribution (Guru Murthy et al. 2018). In the past, due to the lack of definitive diagnostic criteria, it was often misdiagnosed as cutaneous T-cell lymphoma, leukemia cutis, melanoma, or lupus erythematosus. However, a set of widely accepted criteria have been developed to define it (Sapienza et al. 2019; Julia et al. 2013), including blast cells expressing CD4+ and/or CD56+ in lymph node or bone marrow biopsy, at least one positive plasmacytoid dendritic cell marker (e.g., TCL, CD123, BDCA2, CD303/CD2AP, TCF4), and absence of other lineage-specific markers.

Standard treatment regimens and randomized controlled trials for BPDCN are currently lacking. Both high and low intensity chemotherapy regimens approved for lymphoma, and leukemia have been used to treat, including CHOP for lymphoma, Hyper-CVAD alternating with methotrexate and cytarabine for acute lymphoblastic leukemia, 7 + 3, FLAG-IDA and MICE for acute myeloid leukemia (Pagano et al. 2013). Even though, high intensity regimens used for lymphoblastic leukemia are considered more intense, and have shown marginally better outcomes when compared to myeloid leukemia regimens. Venetoclax, a BCL-2 inhibitor, has been used in combination with high intensity regimens to manage (Agha et al. 2018; Pemmaraju et al. 2015), but it has never been used as substitute to other drugs in regimen. As of today, there is no clear guideline on how to manage BPDCN. However, in 2018, the FDA approved tagraxofusp-erzs (SL-401; ELZONRIS™), a targeted therapy that is specifically designed to target the CD123 receptor on BPDCN cells. Tagraxofusp-erzs has been shown to be effective in treating BPDCN, and it is currently the only FDA-approved treatment for the disease (Pemmaraju et al. 2019). Hematopoietic stem cell transplant when in remission has also been shown to improve progression-free survival (Aoki et al. 2015).

Case presentation

A 49-years-old Arab man presented to our institution in January 2022 with a more than one-year history of gradually worsening widespread, painless multiple skin lesions. The patient had previously undergone a biopsy of the left facial lesion elsewhere in May 2021, which was reported as marginal zone lymphoma (MZL). The immunohistochemistry (IHC) results at that time: neoplastic cells were CD79a, CD19, and PAX5 positive B-cells, with strong BCL-2 expression (anti-apoptosis marker), weakly positive for MUM1 (non-specific), and negative for TdT, BCL6, and CD34 (stem cell marker). The PET scan at that time revealed extensive widespread FDG-avid cutaneous/subcutaneous lesions throughout the body, lymphadenopathy of the nasopharynx, chest, and abdomen, left testicle, and bone marrow. Based on these findings, the patient was diagnosed with stage IV MZL and received 2 cycles of bendamustine and rituximab regimen. Subsequent PET scan revealed an excellent partial response (Deauville score 3). However, after two more cycles, the disease relapsed with new lesions and B symptoms. Excisional lymph node biopsy done at this stage showed diffuse expression of T-cell markers (CD3, CD4, and CD43), and lack of all other B-cell markers (CD19, CD20, CD21), stem cell antigens (CD34), and myeloid markers (myeloperoxidase, CD33) with negative EBER (EBV encoded RNA). The results for T-cell and B-cell gene rearrangement studies were negative Therefore, non-specific T-cell lymphoma was considered, and CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) chemotherapy was initiated. However, the disease remained refractory, so the patient was referred to our center. Past medical history included diabetes, peripheral neuropathy, hypertension, and depression.

At our center, initial physical examination revealed a large seven-centimeter disfiguring tumor on the left side of face (Fig. 1A) and multiple, asymmetric, non-tender, erythematous palpable macules, and deep brown to black nodules (Fig. 1B). Furthermore, diffuse painless, firm, discrete lymphadenopathy, and signs of grade 2

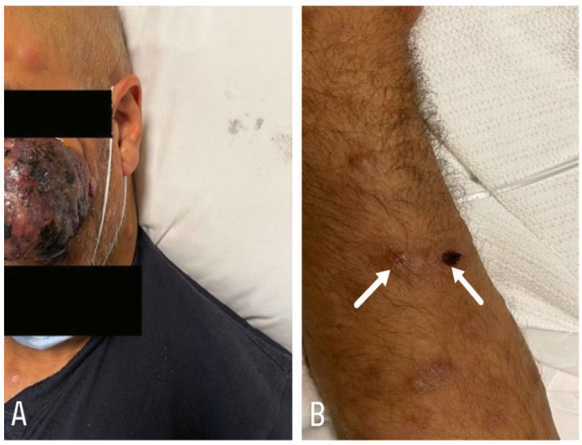

Fig. 1 Blastic plasmacytoid dendritic cell neoplasm. **A** Large facial brownish mass with necrotic patches on the skin. **B** Forearm brownish palpable macules with necrotic patch (arrow)

peripheral neuropathy were noted. Other system exams did not reveal any abnormality.

A comprehensive evaluation was performed. Peripheral blood showed normocytic anemia (Hemoglobin 92 g/L; MCV 94.6 fL) with a normal platelet count (205×10^9/L), and mild neutropenia (1.34×10^9/L). Bone marrow examination revealed plasmacytoid dendritic cells with unique finding of signet ring cell morphology (Fig. 2). Concurrent lymph node examination, including IHC using multiple lineage markers, showed neoplastic blastoid cells that were CD123/CD303-positive, co-expressing CD4, TCL1A, strong aberrant expression of CD56 (Fig. 3), and negative for the remaining markers evaluated. T-cell lymphoma was ruled out based on negative CD3, CD5, CD7, and CD8. A B-cell lymphoma was excluded based on negative CD19 and CD20, Hodgkin lymphoma based on negative CD30, stem cell disease [CD34], and myeloid malignancy based on negative CD64, CD68, CD117, and MPO. The PET scan revealed increased abnormal FDG uptake on the left side of the face, skin, and cervical plus inguinal lymph node. Karyotype and FISH panels showed no chromosomal aberrations. New generation sequencing (NGS) revealed a KRAS p.G12D mutation.

Considering neuropathy and earlier treatment planned to provide the only FDA-approved drug, the anti-CD123 cytotoxin Tagraxofusp. Due to challenges in procurement of this drug and rapidly proliferating skin lesions we administered Hyper-CVAD (lymphoblastic leukemia regimen) regimen. We had to reduce vincristine dose by fifty percent during cycle one, part

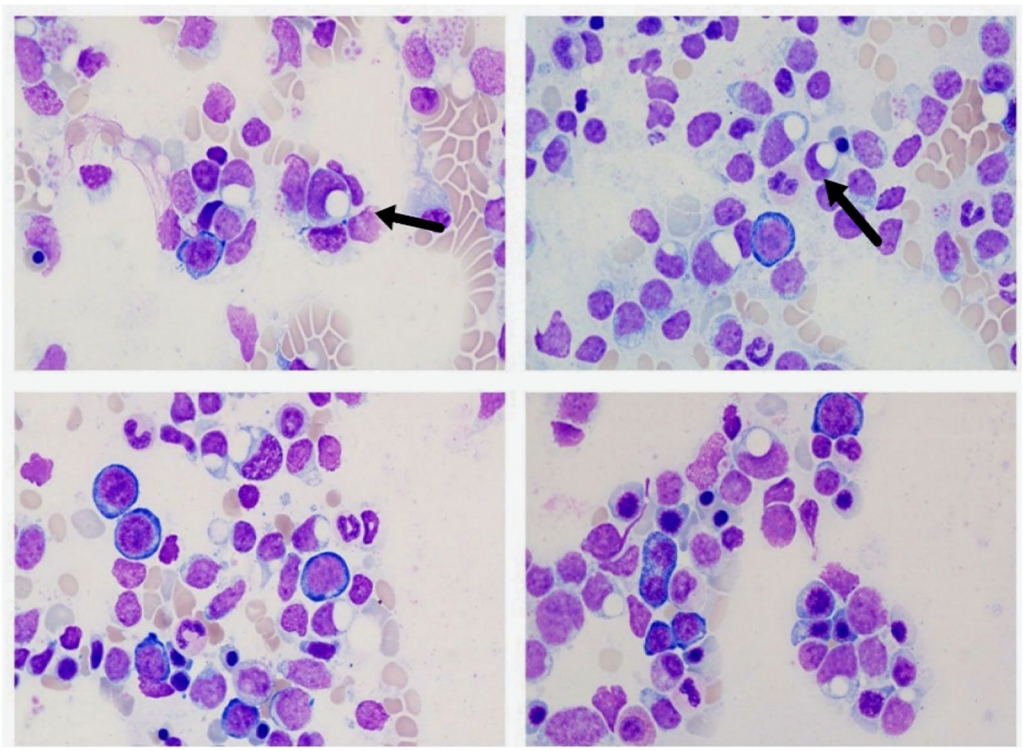

Fig. 2 Blastic plasmacytoid dendritic cell neoplasm. Cells frequently show previously undescribed signet ring cell morphology (arrow). Bone marrow aspirate, 600× magnification

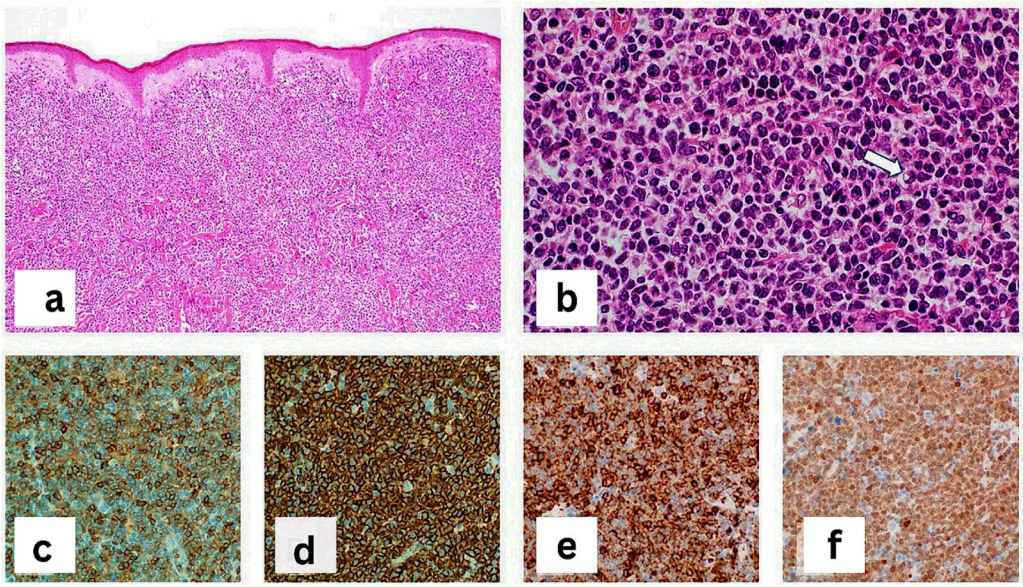

Fig. 3 Blastic plasmacytoid dendritic cell neoplasm. **A** Extensive skin involvement by tumor 40× magnification; **B** Tumor cells in lymph node with brisk mitotic activity and a rare cell showing signet ring cell morphology (arrow, 400× magnification); **C**, **D**, **E** and **F** Tumor cells showing positive immunohistochemical staining for CD4, CD56, CD123 and TCL 1A respectively (lymph node, 400× magnification)

one due to severe pain, numbness and mild weakness related to pre-existing neuropathy. Intrathecal chemotherapy was administered for CNS involvement. Excellent clinical response was observed after part one of the first cycle. On the third day of cycle one, part two treatment, we noticed new lesions and an increase in size of earlier regressing skin tumors. We added venetoclax, a BCL-2 inhibitor, on the fourth day of cycle one part two and the patient received it for 2 weeks. CT scan showed a reduction in the size of face lesions, cervical, and inguinal lymph nodes. Unfortunately, pain, numbness and weakness related to neuropathy (Nerve conduction studies show severe polyradiculopathy) worsened so vincristine was completely removed from his protocol during the second cycle, part one and venetoclax continued. New skin lesions began to fade, and the existing ones regressed completely. Subsequent PET scan after cycle 2 confirmed a complete clinical and radiological response as seen in Fig. 4.

The patient presented six weeks later with relapse and bone marrow transplant was deferred. We procured and initiated tagraxofusp but had to discontinue its use on the fourth day due to grade 3 liver toxicity (AST: 403IU/L, ALT: 153IU/L). Further management became difficult due to the rapid progression of skin lesions, liver toxicity, seizures, and cytopenias. Eventually, the patient succumbed in September 2022, seventeen months after the initial diagnosis of malignancy.

Discussion

This case report highlights a number of issues in the diagnosis and treatment of this cancer. Diagnosis can be challenging due to its rarity and the overlap of clinical and morphological features with other hematological malignancies involving skin. Clinical and morphological suspicion is crucial in directing the specialized cell marker studies required to confirm the diagnosis (CD123, BDCA2, CD303/CD2AP, TCF4) (Orazi et al. 2013). Additionally, the blastic pDCs were frequently of signet ring cell shape on the aspirate smears, a feature that is hitherto undescribed.

Treatment remains challenging, but high-intensity regimens such as Hyper-CVAD, which includes vincristine, are now being considered as the standard of care (Chaperot 2001; Pagano et al. 2013; Montero et al. 2017). However, the development of new-onset neuropathy or worsening of pre-existing neuropathy can significantly limit the use of these regimens. In this particular case, the patient's vincristine dose had to be reduced by fifty percent during cycle one and completely omitted during cycle two due to the manifestation of significant neuropathy. As the disease relapsed during the latter part of cycle one treatment, we were faced with the need to select a drug that could sustain remission with minimal side effects. Venetoclax, a BCL-2 inhibitor, emerged as the most promising alternative due to its demonstrated favorable outcomes

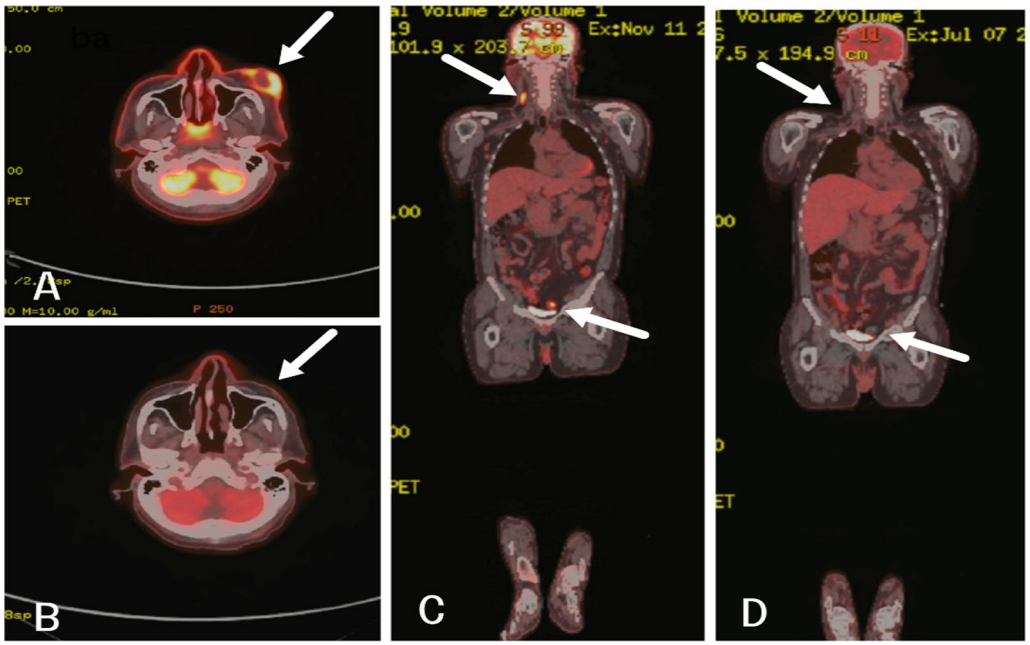

Fig. 4 **A**, **B** Axial PET-CT increased tracer uptake left facial lesion (arrows) and complete resolution of same post treatment respectively. **C**, **D** coronal PET-CT, increased tracer uptake in cervical and inguinal lymph node (arrows) and complete resolution of same post-treatment

when combined with high-intensity regimens (Pemmaraju et al. 2015; Agha et al. 2018). In a similar context, venetoclax has been successfully used as a substitute for vinorelbine, a member of the same drug class as vincristine, in the management of diffuse large B-cell lymphoma (DLBCL), exhibiting excellent safety and favorable outcomes (Hatzl et al. 2021). Although no reported cases of BPDCN utilizing venetoclax as a substitute for vincristine exist to date, our patient demonstrated a maintained response for an additional six weeks before experiencing disease relapse during a treatment break while preparing for a stem cell transplant from a fully matched related donor.

We also attempted the use of tagraxofusp, a CD123-directed cytotoxin and the first FDA-approved treatment for BPDCN. However, its administration was limited due to rapid onset grade 3 hepatotoxicity, thrombocytopenia, and peripheral edema (Pemmaraju et al. 2019). Despite the challenges encountered in procuring the drug, the patient could only receive a partial dose. Nevertheless, the patient's survival for a duration of seventeen months slightly exceeds the reported overall survival in similar cases (Wang et al. 2018). Despite surviving better than reported cases, the patient experienced significant psychological distress due to skin lesions. The only time he felt blissful was during the 6 weeks he did not have any skin lesions. This was the only time in his entire 17-month journey that he felt relieved.

Conclusion

In conclusion, accurate diagnosis and modified treatments are crucial to address the challenges of BPDCN. Misdiagnoses underscore the need for heightened awareness and comprehensive evaluations. We suggest lowering the threshold for complete re-evaluation when immunohistochemical marker studies are ambiguous and minimal or no response to standard chemotherapy regimens is observed. Vincristine limitations due to neuropathy prompted the use of venetoclax as a substitute, showing promise. However, the patient's relapse highlights the aggressive nature of the disease, necessitating further research on BCL-2 inhibitors as replacements and bridging therapy to stem cell transplant. The lone indication, high side effect profile, and difficulty in procuring Tagraxofusp, the only FDA-approved drug for BPDCN, may limit its usage in real-world settings. More studies are needed to see the drug's true adaptability in real-world patients. Enhancing treatment options and outcomes for this rare neoplasm remains a vital goal.

Abbreviations

BPDCN	Blastic plasmacytoid dendritic cell neoplasm
pDC	Plasmacytoid dendritic cells
CD	Cluster of differentiation
BCL2	B-cell lymphoma-2
BDCA2	Blood dendritic cell antigen 2
TCL	T-cell leukemia
TCF4	Transcription factor 4

CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
Hyper-CVAD	Hyper fractionated-cyclophosphamide, vincristine, doxorubicin, dexamethasone
MZL	Marginal zone lymphoma
IHC	Immunohistochemistry
PET	Positron emission tomography
CNS	Central nervous system
FDA	Food and Drug Administration
DLBCL	Diffuse large B-cell lymphoma

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Author contributions
NS is part of the treating team, drafted the manuscript, conducted the literature review, analyzed the patient data, and finalized the manuscript. WJ is part of the treating team, obtained consent from the patient, and provided clinical images. ISE helped in drafting the initial manuscript and is part of the treatment team. IM provided pathology images, contributed to the analysis and interpretation of the pathology data, and edited the manuscript. DM is part of the treating team, supervised the case report, contributed to the manuscript writing, reviewed and edited the final manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
I confirm that the patient consent has been signed and collected in accordance with the journal's patient consent policy. I will retain the consent form and will provide it if requested. As required, patient anonymity has been preserved throughout this manuscript.

Consent for publication
I confirm that the patients involved in this manuscript provided consent for publication in accordance with the journal's patient consent policy.

Competing interests
All contributing authors declare that they have no conflicts of interest, including any specific financial interests, relationships, or affiliations relevant to the subject matter or materials discussed in this manuscript.

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References

Agha ME, Monaghan SA, Swerdlow SH (2018) Venetoclax in a patient with a blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 379(15):1479–1481
Aoki T, Suzuki R, Kuwatsuka Y, Kako S, Fujimoto K, Taguchi J et al (2015) Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. Blood 125(23):3559–3562
Chaperot L (2001) Identification of a leukemic counterpart of the plasmacytoid dendritic cells. Blood 97(10):3210–3217
Guru Murthy GS, Pemmaraju N, Atallah E (2018) Epidemiology and survival of blastic plasmacytoid dendritic cell neoplasm. Leuk Res 73:21–23
Hatzl S, Posch F, Rezai A, Gornicec M, Beham-Schmid C, Magnes T et al (2021) Vinorelbine as substitute for vincristine in patients with diffuse large B cell lymphoma and vincristine-induced neuropathy. Support Care Cancer 29(9):5197–5207
Julia F, Petrella T, Beylot-Barry M, Bagot M, Lipsker D, Machet L et al (2013) Blastic plasmacytoid dendritic cell neoplasm: clinical features in 90 patients. Br J Dermatol 169(3):579–586
Khoury JD (2018) Blastic plasmacytoid dendritic cell neoplasm. Curr Hematol Malig Rep 13(6):477–483
Montero J, Stephansky J, Cai T, Griffin GK, Cabal-Hierro L, Togami K et al (2017) Blastic plasmacytoid dendritic cell neoplasm is dependent on BCL2 and sensitive to venetoclax. Cancer Discov 7(2):156–164
Orazi A, Foucar K, Knowles D, Weiss LM (2013) Plasmacytoid dendritic cell neoplasms. Knowles neoplastic hematopathology, 3rd edn. Lippincott Williams & Wilkins, Philadelphia
Pagano L, Valentini CG, Pulsoni A, Fisogni S, Carluccio P, Mannelli F et al (2013) Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 98(2):239–246
Pemmaraju N, Kantarjian HM, Cortes JE, Duvic M, Khoury JD, Patel K et al (2015) Blastic plasmacytoid dendritic cell neoplasm (BPDCN): a large single-center experience: analysis of clinical and molecular characteristics and patient outcomes. Blood 126(23):3746–3746
Pemmaraju N, Lane AA, Sweet KL, Stein AS, Vasu S, Blum W et al (2019) Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med 380(17):1628–1637
Sapienza MR, Pileri A, Derenzini E, Melle F, Motta G, Fiori S et al (2019) Blastic plasmacytoid dendritic cell neoplasm: state of the art and prospects. Cancers (basel) 11(5):595
Wang S, Wang X, Liu M, Bai O (2018) Blastic plasmacytoid dendritic cell neoplasm: update on therapy especially novel agents. Ann Hematol 97(4):563–572

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