



Blastic Plasmacytoid Dendritic Cells neoplasia Case report: Considerations and challenges

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BACKGROUND

Plasmacytoid Dendritic Cells (pDCs) are hematopoietic cells, type1 interferon natural producing cells. Under normal conditions, these cells constitute less than <1% of total nucleated cell population in peripheral blood and bone marrow. Neoplastic expansion of these cells is very rare form of a leukemia/lymphoma and it is classified into 2 different malignancies: **Blastic Plasmacytoid Dendritic Cells Neoplasm (BPDCN)** and **mature pDCs proliferation associated with myeloid neoplasia (MPDCP)**. Clonal expansion of pDCs has been well described in chronic myelomonocytic leukemia, while their expansion in the context of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) has just begun to unfold. **BPDCN** is well defined entity, which was formerly assigned to AML and related precursor neoplasms (as per 2008 World Health Organization Classification of Hematological Diseases), but separated as distinct entity in the revised classification in 2017. It is a very rare type of leukemia, comprising for <1% of all hematological malignancies. MPDCP is not referenced in WHO classification, except as differential diagnosis of BPDCN. However, distinguishing these two conditions can be extremely challenging due to overlapping clinical and histological features. Therefore, extended immuno-histochemical analyses and immunophenotyping are mandatory for establishing correct diagnosis. Both entities predominantly affect males (>75%) with a median age of 69 years¹. It is characterized by aggressive clinical course and rapid systemic spread, often presenting with skin lesions and extramedullar involvement. Here we present the diagnostic challenge of a rare case of BPDCN from our practice.

Objective: Case specificity, dilemmas & challenges summary

• Our object is to present our first experience with a very rare case of BPDCN, which was a diagnostic challenge in **various aspects**. First of all, the reported patient is a **young 26-year-old male**, who presented with gradually progressive cytopenia. Secondly, **he lacked skin lesions and other extramedullar manifestations**.

• Then, **initial bone marrow biopsy suggested metastatic ectodermal neoplasia**, which misled us and we performed further radiographic procedures to rule out the diagnosis. At this time, we were unable to obtain bone marrow aspirate.

• **Contra lateral bone marrow aspiration and biopsy** was performed a month later and both immunohistological staining and flow cytometry phenotype suggested **BDPCN**, as discussed in detail above. Still, due to unusual presentation and rarity of this diagnosis itself and more limited immunohistochemical analyses, **bone marrow tissue was sent for consultative opinion in reference centre (Institut für Pathologie -Universität Würzburg)**. Considering the aggressive biology of the disease, we initiated treatment before having the final response. We have almost no former experience with this disease, therefore, we followed **MD Anderson recommendations on BDPCN** and the patient was treated with ALL-based chemotherapy regimen in combination with bcl-2 inhibitor.

• The reference centre histological examination **concluded diagnosis of AML rather than BDPCN based on negativity of TCL1**, described in detail further, facing us with the **final dilemma** of further treatment strategy. However, hematological remission was achieved after one cycle therapy, which played the decisive role to continue treatment with the same ALL- based chemotherapy regimen. The patient is +60 days after MUD transplant and still in **remission**

DIAGNOSTIC WORKUP AND PROCEDURES – CASE REPORT AND LITERATURE DATA

Clinical and laboratory findings:

Medical History: A previously healthy 26 year-old man presented with a 1-month history of weakness, malaise and myalgia.

Clinical examination: He had no evident cutaneous lesions, nor organomegaly, nor lymphadenopathy.

Laboratory findings: Initial blood counts and peripheral blood smear showed normocytic anemia (Hb 103 g/L) and leukopenia (WBC 2,4 x 10³ u/L) with dominant lymphocytosis. Biochemistry analyses were within normal ranges, except for slightly elevated AST and LDH. He was referred to infectious disease specialist and a viral etiology was excluded.

At the control visit 2 weeks later, he did not complain of any new symptoms. He had no signs of hemorrhagic syndrome. Blood counts showed **severe leucopenia** (WBC 0,8 x10³/ u/L) and **thrombocytopenia** (PLT 18 x 10³ u/L). Still, peripheral blood smear did not reveal any atypical cells. He was hospitalized for further investigations.

Initial bone marrow investigation – “false track”

On suspicion of acute leukemia or aplastic anemia, bone marrow biopsy was performed. Bone marrow aspirate was not obtained. Histological examination indicated metastatic nasopharyngeal carcinoma. As a result, he underwent detailed ENT examination and except for nodular lymphoid tissue in epypharinx, no other abnormalities were observed. Additionally, MRI of the neck with contrast was performed and showed normal findings. In consultation with otolaryngologist, this diagnosis was ruled out.

Histological examination of contra lateral bone marrow biopsy – Reference centre opinion

Histological examination of the contra lateral bone marrow tissue was consistent with our immunophenotypic findings. HE and Giemsa histological staining showed nearly complete infiltration of an atypical blastoid cell population (figure 1, figure 2-3). **Immunohistochemically**, cells were **positive for CD56, CD4** (figure 4 and 5), **CD33 and CD117**. This findings concluded the diagnosis of BPDCN.

Still, due to limited experience and resource-limited staining settings, **bone marrow tissue was sent for consultative opinion in reference centre – Referenzzentrum für Lymphknotendiagnostik Institut für Pathologie – Universität Würzburg**.

An extended immunohistochemical profile was analyzed. The stainings for CD3, CD5, CD7, CD8, Perforin, TdT, PAX5, CD10, CD138, kappa, lambda, CD34, CD30, ALK1, AE1/AE3 were negative. Ki67 proliferation index was 80%.

TCL1 staining was negative. In consideration of the TCL1 negativity, this findings were rather conclusive for AML than BDPCN.

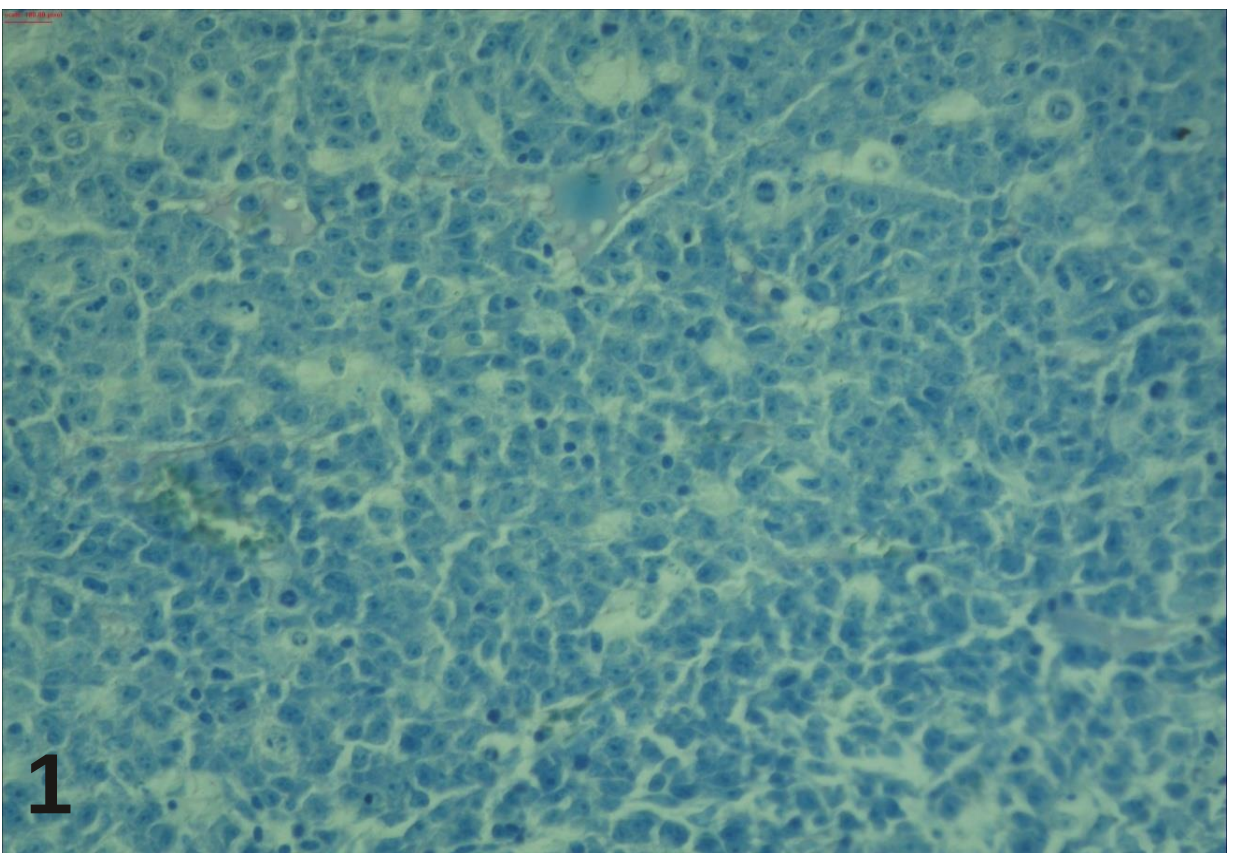


Figure 1 - Tumor cell morpholgy (Giemsa x 200)

Immunophenotyping by flow cytometry – first suspicion on BPDCN

One month of the initial bone marrow biopsy, a contra lateral bone marrow biopsy and aspiration was performed.

BM aspirate was analysed with **Multiparameter flow cytometry immunophenotypic study**. For data acquisition, a *FACSCanto II flow cytometer and FACSDiva Software* was used. We applied ELN recommended panel of monoclonal antibodies for acute leukemia. However, this is the standard panel for classifying acute leukemia into acute myeloid leukemia and acute lymphoblastic leukemia and does not include all the monoclonal antibodies, required for the diagnosis of BPDCN.

Immunophenotypic study showed **50% infiltration with homogenous cell population with weak expression of CD45**. These cells **were HLA-DR positive** and had **no expression of CD34**. The cells showed **coexpression of CD4/CD56**. Additionally, **low expression of myeloid markers CD33 and CD117** was noted.

In line with reported studies, **the diagnosis of BPDCN by immunophenotype is very well defined by the presence of CD4+, CD56+, CD123+, CD303+/-, CD304+/-, TCL1 + blasts²**. Therefore, we additionally analyzed bone marrow for CD123, but we were unable to test for CD303, CD304 and TCL1. Analyzed cells had **high expression of CD123**.

This immunophentype posed the first suspicion on BDPCN. Despite this very typical immunophenotypic pattern of BDPCN, our insufficient experience and more limited analyses, we could not confirm the diagnosis with absolute certainty.

Extended immunophenotyping is mandatory for the diagnosis of BPDCN. MPDCP should always be considered as differential diagnosis of BPDCN, as these diagnoses although clinically similar, require different therapeutic approach. Both diagnoses predominantly occure in male and elderly patients, while skin lessions are less frequent in MPDCP¹.

• **Normal human pDC** are identified by flow cytometry based on high expression of CD123, HLA-DR and CD303 in absence of the other lineage markers, described above.

• On the other hand, **pDC phenotype in MPDCP** is poorly described. However, in contrast do BDPCN, atypical cells in MPDCP are heterogenous. According to more recent studies^{2,3}, blastic population of myeloid lineage is the dominant population. Associated pDCs have high expression of CD123, CD4+, low expression of CD303, CD304, but in contrast to BPDCN, they are **typically negative for CD56 and show low expression for CD34**.

• *In Table 1, we summarized th immunophenotypic features of BPDCN and pDC in MPDCN in line with published data.*

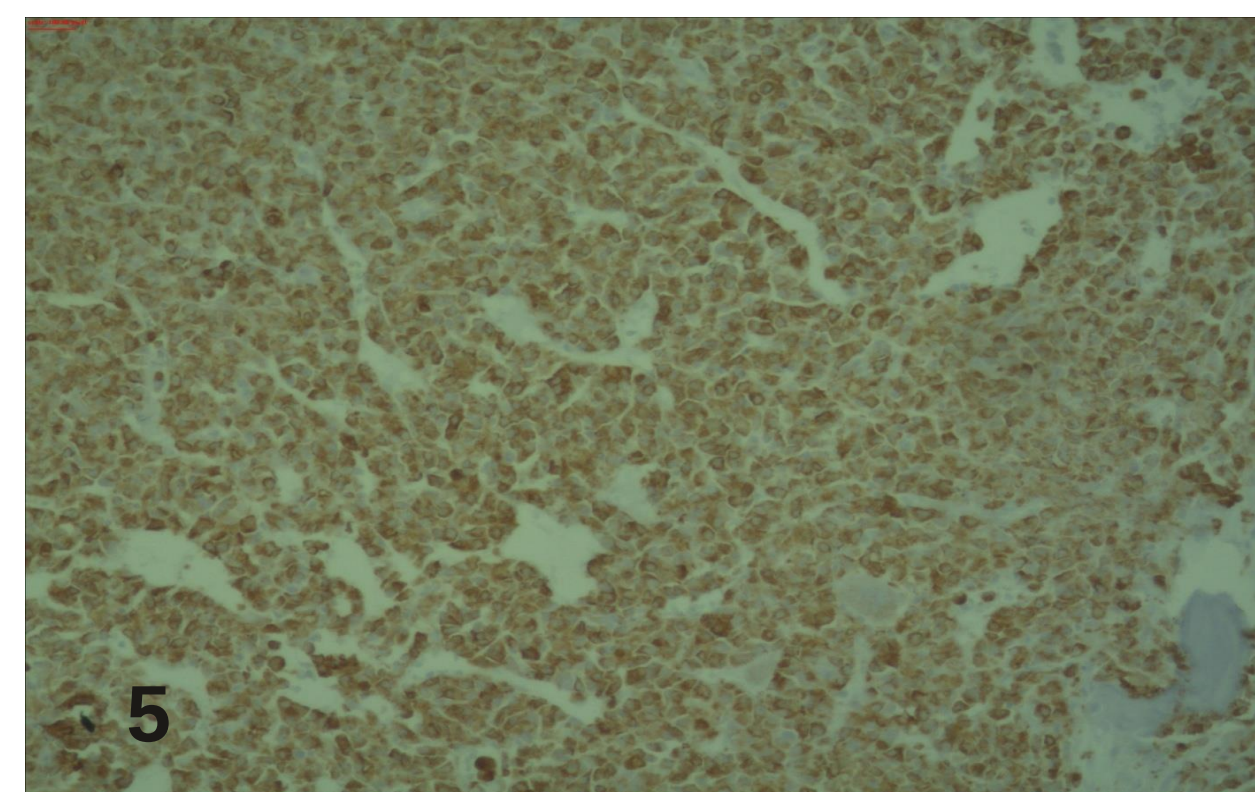
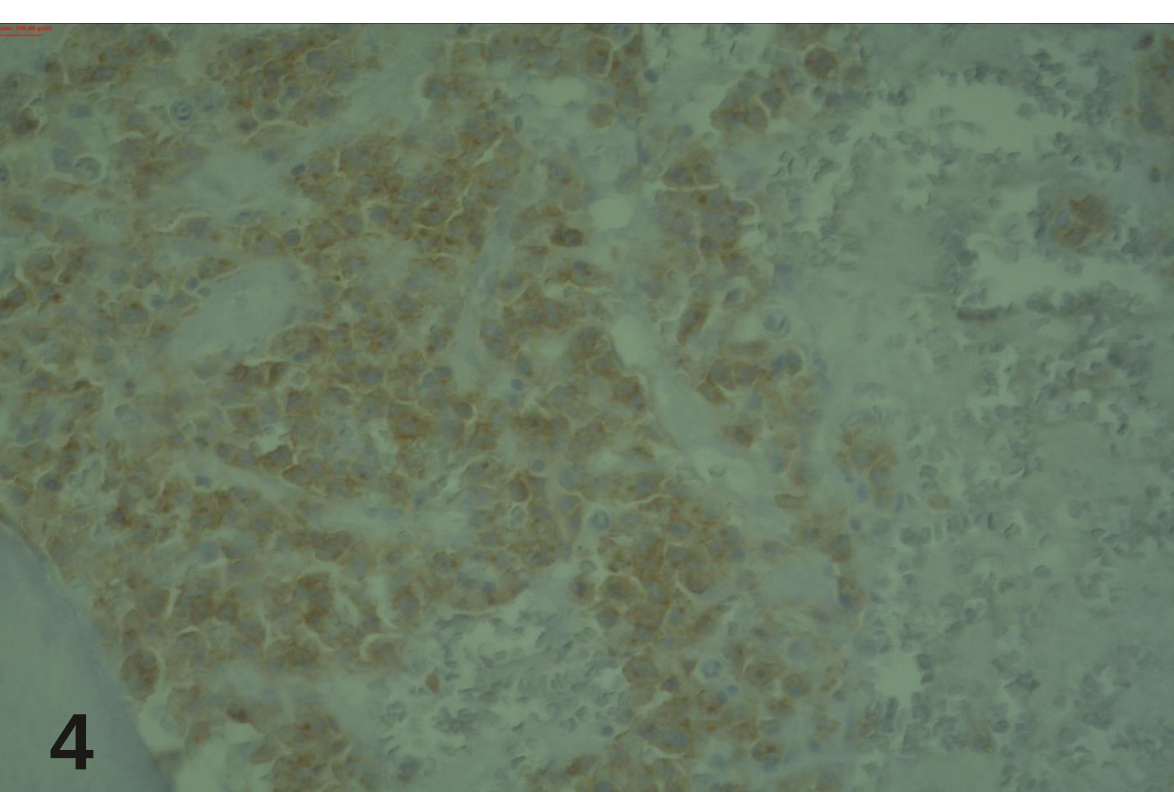
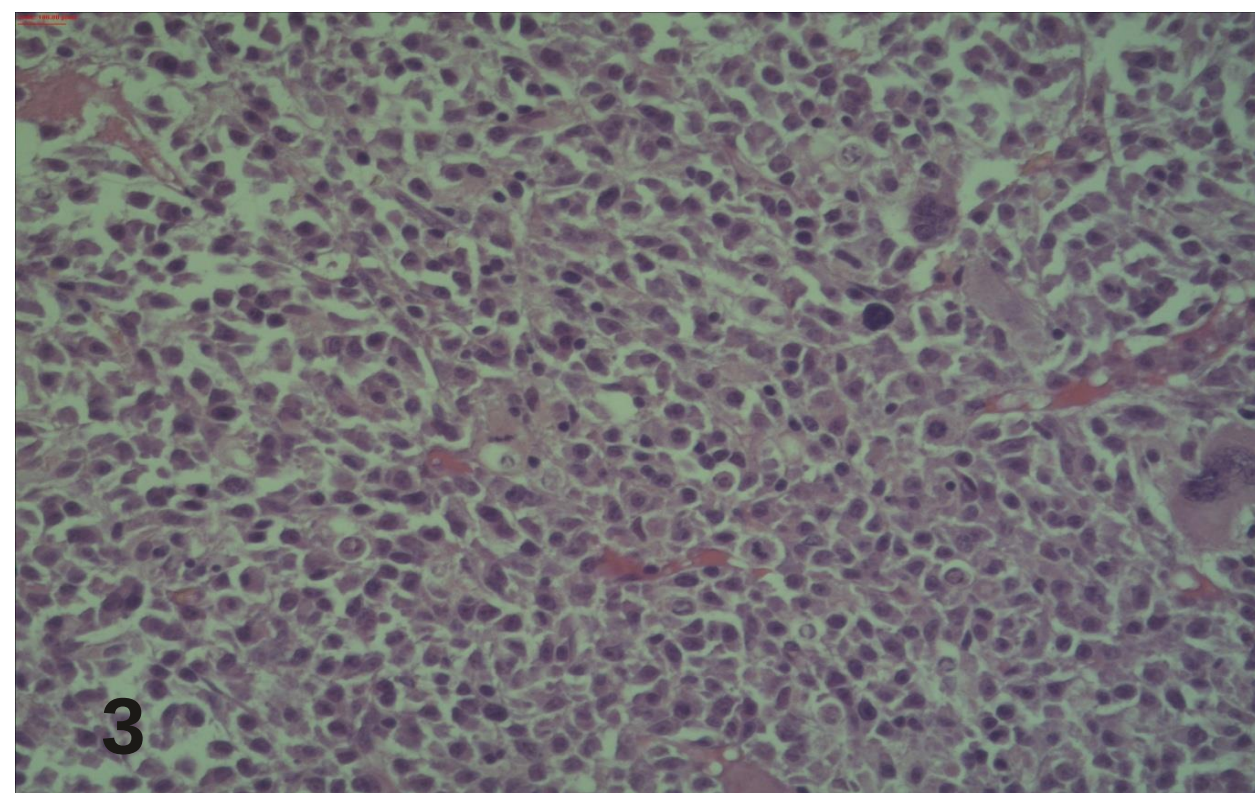
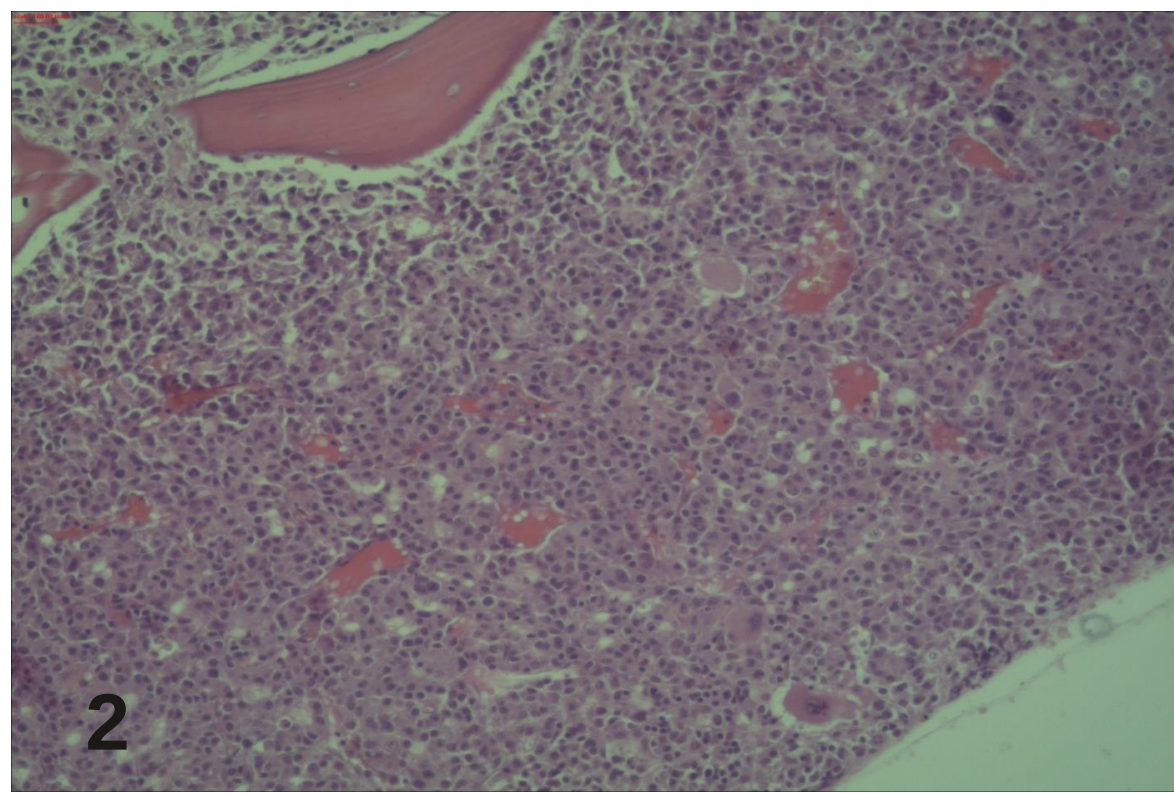


Figure 2-3 Tumor cell morphology (Hematoxinilin&Eosin x 100; x200)

Figure 4-5 Immunohistochemical Stainings: Figure 4- CD4+; Figure 5 - CD56+

mAB	BDPCN	pDC in MPDCN
CD45	±low	±low
CD34	-	-/+
HLA-DR	±high	±high
CD303	-/+	-/+
CD304	-/+	-/+
CD123	±high	±high
CD4	±high	±high
CD56	±high	-
CD117	-/+	-/+
CD33	-/+	-/+
CD 13	-/+	-/+
TdT	-/+	-/+
cTCL1	±high	-/+

Table 1 – Main Immunophenotypic features of BPDCN and pDC in MPDN
Key discriminates are given in red.

Mutation profile

PDC-AML is characterized by frequent RUNX1 mutation (over 75% of these patients have RUNX1 aberation. In contrast to this, only <5% of BPDCN cases are associated with RUNX1 mutation. In this patient, neither RUNX1 mutation was detected, nor other prognostic markers for AML.

TREATMENT CONSIDERATIONS

Taking into account the aggressive course of the disease and the poor prognosis, we initiated treatment before obtaining the result from the Reference centre. We followed *MD Andersson Cancer Centre treatment approach and Hyper-CVAD regimen plus Venetoclax* was initiated.

Venetoclax at a dose of 100 mg/ day 1-day 14 each cycle was administrated. After the course A of the first cycle chemotherapy, complete recovery of hematological parameters was achieved, while remission was achieved after the first cycle (course A and course B).

Therefore, independently of histological findings, we continued treatment with one more cycle Hyper-CVAD + Venetoclax followed by matched unrelated donor stem cell transplantation.

CNS prophylaxis: There is a strong association of BPDCN with CNS involvement. Although no clinical nor cytological signs of CNS involvement was observed in this patient, he received additional doses of intrathecal chemotherapy.

References:

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- Zalmaï L, et al.. Plasmacytoid dendritic cells proliferation associated with acute myeloid leukemia: phenotype profile and mutation landscape. Haematologica. 2020
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