



Case Report

Indispensable role of immunophenotyping in diagnosing leukemic phase of blastic plasmacytoid dendritic cell neoplasm without cutaneous manifestation

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ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm usually presents as skin lesions. Diagnostic error occurs when it primarily presents in leukemic phase without skin involvement. Triad of CD4, CD56 and CD123 immunophenotype expression is essential to avoid misdiagnosis of this rare hematological malignancy. Here we describe a patient who presented in overt leukemic phase of BPDCN highlighting diagnostic challenges encountered that resulted in delayed diagnosis and poor outcome.

1. Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematologic cancer that arises from plasmacytoid dendritic cells (pDC) [1]. It most commonly manifests as violaceous bruise-like cutaneous lesions followed by involvement of hematolymphoid tissues [2]. Overall, the incidence is extremely low, accounting for only 0.44 percent of all hematologic malignancies. Most patients present in their sixth and seventh decade of life with well-documented male predominance [3].

In rare instances it primarily presents in acute leukemic phase involving bone marrow with variable degree of cytopenia. No characteristic cytogenetic or molecular abnormality is found in BPDCN and circulating neoplastic pDC can be easily mistaken for lymphoblast or myeloblast, therefore, the diagnosis of leukemic phase is heavily dependent on immunophenotyping [4]. Immunophenotyping shows characteristic triad of positive expression of C4, CD56, CD123 and absence of B-cell, T-cell, NK-cells and myeloid lineage specific markers [4]. Making an early diagnosis without incorporation of immunophenotyping is therefore challenging. In 2008, World Health Organization enlisted BPDCN under category of “acute myeloid leukemia and related precursor neoplasm”, however in 2016, it has been identified as separate entity [5].

Despite treatment including hematopoietic stem cell transplantation

prognosis is poor, except for isolated skin involvement that tends to do better. Due to rarity of this disease, there is no agreed-upon standard treatment. Recently, Tagraxofusp-erz (the first ever CD123-targeted agent) has been approved for treatment of BPDCN but is associated with life-threatening toxicity [6].

Herein, we describe a case of an elderly man who was misdiagnosed as non-Hodgkin's lymphoma on initial bone marrow examination and then as acute leukemia on morphological examination of peripheral blood smear, before being correctly diagnosed as leukemic BPDCN.

2. Case

A 73-year-old man was referred to our hospital with a four-week history of generalized weakness, abdominal pain, nausea, and vomiting. Physical examination revealed pallor, axillary lymphadenopathy and splenomegaly. No skin lesions were found. Past medical history was unremarkable. He has had his bone marrow biopsy done a week earlier, at the referring hospital which was reported as non-Hodgkin's lymphoma and subsequently acute myeloid leukemia was favored on peripheral blood smear morphology. Since there was a discrepancy between the two reports, the diagnostic workup was re-evaluated at our facility. A repeat CBC showed Hb: 9.4 g/dl, Hct: 29.7%, Wbc: $12 \times 10^9/L$, ANC $1.3 \times 10^9/L$ and platelets $18 \times 10^9/L$. Peripheral blood smear was leucoerythroblastic with presence of 40% atypical cells closely

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mimicking blast cells (Fig. 1a). Renal function was normal, but liver function was deranged [total bilirubin 5.5 mg/dl (0.1–1.2), direct bilirubin 3.8 mg/dl (0–0.2)] with elevated transaminases. Bone marrow smears, and trephine block were requested to be reviewed by our hematopathologist which showed aspicular, hemodiluted specimen exhibiting few atypical cells with eccentric nucleus, fine nuclear chromatin and weakly basophilic, agranular cytoplasm with pseudopods (Fig. 1b). Bone trephine showed diffuse infiltration with suppression of normal haematopoiesis (Fig. 1c).

Based on peripheral blood smear and bone marrow morphological findings immunophenotyping on peripheral blood was done. Immunophenotyping of CD45^{dim} positive cells (35%) within blasts gate (performed on BD FACSCanto™ II analyzer, 8 color and 3 lasers) revealed positivity to CD33 (29%), HLA-DR. (35%), CD4 (35%), CD7 (32%) CD123 (35%) and CD56 (35%) but negative for other lineage-specific markers (like CD19, CD79a, CD22, CD10, cytoplasmic and surface CD3, CD5, CD8, MPO, CD13, CD14, CD64, CD36, kappa/lambda light restriction, Tdt, CD34 (Fig. 2& 3).

Extended panel of B-cell markers (CD19, CD22) are negative. T-cell markers show positive expression of CD4 and CD7.

CT scan showed bilateral axillary and abdominal lymphadenopathy, splenomegaly and cholelithiasis. Histopathology of axillary lymph node also exhibited cellular infiltrate with moderate atypical plasmacytoid cytoplasm and elongated hyperchromatic nuclei, expressing LCA, CD43, CD4, CD56 with high proliferation index and negative for CD34, CD30, PAX-5, CD68, CD19, CD20, MPO, CD117, and MUM1. pDC-specific immunohistochemistry markers were not performed due to non-availability. Since all lineage specific markers were negative except for LCA, CD43, CD4 and CD56, and in conjunction with morphology and immunophenotyping on blood, a diagnosis of BPDCN was made. Cytogenetics and molecular studies were not sent as it was refused by the patient. Due to poor performance status, intensive chemotherapy was deferred and azacytidine along with allopurinol was started. On day 3+ of azacytidine patient's clinical condition deteriorated and went into tumor lysis syndrome and acute renal failure. A session of hemodialysis was performed but patient's condition was deteriorated, so the level of care was shifted to palliation after discussion with the family. Consequently, the patient died on day 4 of treatment (10th day of hospital admission).

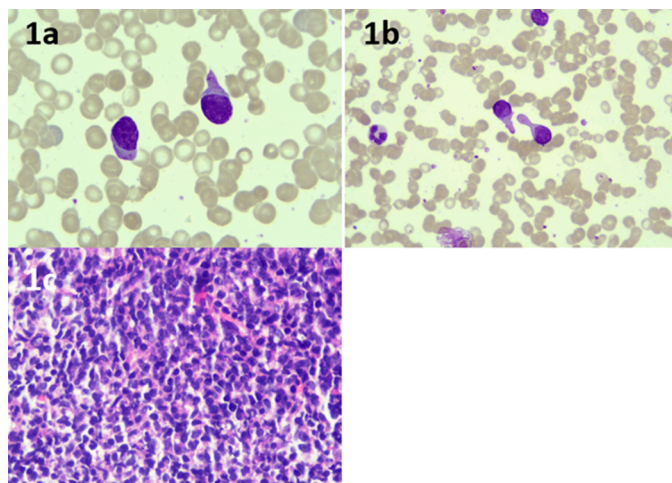


Fig. 1. Peripheral blood smear showing blast-like cells exhibiting cytoplasmic pseudopods (100x) (a). Bone marrow aspirate (40x) showing infiltration with atypical cells with eccentric nucleus, fine nuclear chromatin and weakly basophilic, agranular cytoplasm with pseudopods (b). Bone trephine H&E (40x) showing diffuse infiltration with atypical cells and suppression of normal haematopoiesis (c).

3. Discussion

The rarity of BPDCN makes it difficult to diagnose amongst hematological malignancies, especially when it presents in leukemic phase. In most cases BPDCN arises de novo and in up to 20% there is a prior history of myeloid malignancy like myelodysplastic syndrome, chronic myeloid leukemia, chronic myelomonocytic leukemia, and acute myeloid leukemia [3].

Approximately 75% of patients, present with isolated skin lesions followed by lymphadenopathy and splenomegaly and may later progress to involve other systemic organs [7]. Since skin manifestation is most common, the diagnosis is usually made on skin biopsy with characteristic histological features. When bone marrow is involved, patient may present with cytopenia and circulating malignant cells may be detected in peripheral blood. The malignant cells may exhibit microvacuoles along the cell membrane giving “pearl necklace” appearance and pseudopod-like cytoplasmic extensions, however these changes may sometimes be so subtle that they often get overlooked or be mistaken with “hand-mirror” appearance of lymphoblasts. However, in most instances they mimic poorly differentiated, intermediate-sized blast cells. Therefore, whenever patient presents in primary leukemic phase without cutaneous lesions, the diagnosis is often mistaken with acute leukemia [8].

Hence, the role of immunophenotyping by flowcytometry is crucial in making a diagnosis as these tumor cells typically express CD43, CD4, CD56 and one or more markers of PCD like CD123, BDCA-2/CD303, TCL1 and SBIP [4]. It is important to incorporate PCD markers in immunophenotype panel specially when most of the lineage specific markers are negative.

Similarly, it is important to exclude the expression of other lineage specific markers like lymphoid, myeloid, monocyte before making a diagnosis of BPDCN [4].

In our case, the patient was misdiagnosed on two occasions, before presenting to our facility. So, in the best interest of time considering patient's clinical condition, immunophenotype was performed on peripheral blood. The immunophenotype displayed a distinct cell population of abnormal cells. In this case, MPO, CD64, CD14 and CD34 were negative ruling out the acute myeloid leukemia. CD4 was positive however negativity of lineage-specific marker CD3 and Tdt excluded the possibility of T-lymphoblastic lymphoma/leukemia. None of the B-cell markers were positive. The possibility of mature plasmacytoid dendritic cell proliferation was ruled out based on CD56 positive expression. The tumor cells expressed CD4 and CD56 along with CD123. At our facility, we rely on expression of CD123 in addition to CD4 and CD56.

In rare instances CD56 would not be expressed, but still the diagnosis can be made if there is expression of CD4, CD123 and TCL1. In up to 50% of the cases Tdt and CD68 may be expressed, however the latter is expressed weakly and shows dot-like positivity in the Golgi zone [9]. Lymph node biopsy was performed to consolidate the diagnosis and to rule out and differentiate it from other hematological malignancies that exhibited similar pattern of immunohistochemistry as that of immunophenotyping by flowcytometry.

There are several case reports in the literature where diagnosis of leukemic phase has been mistaken with a wide range of other hematological disorders and patients received unnecessary treatment [10].

Unfortunately, in this case, the patient's clinical condition was rapidly deteriorated by the time the diagnosis was confirmed, making aggressive chemotherapy option undesirable.

The outcome might have been better if the immunophenotyping by flowcytometry has been incorporated early in the diagnostic workup.

This case consolidates the fact that the diagnosis of leukemic BPDCN cannot be made in isolation, incorporating clinical presentation with bone marrow examination and careful evaluation of immunophenotyping with exclusion of myeloid and lymphoid neoplasm is essential for timely diagnosis and management.

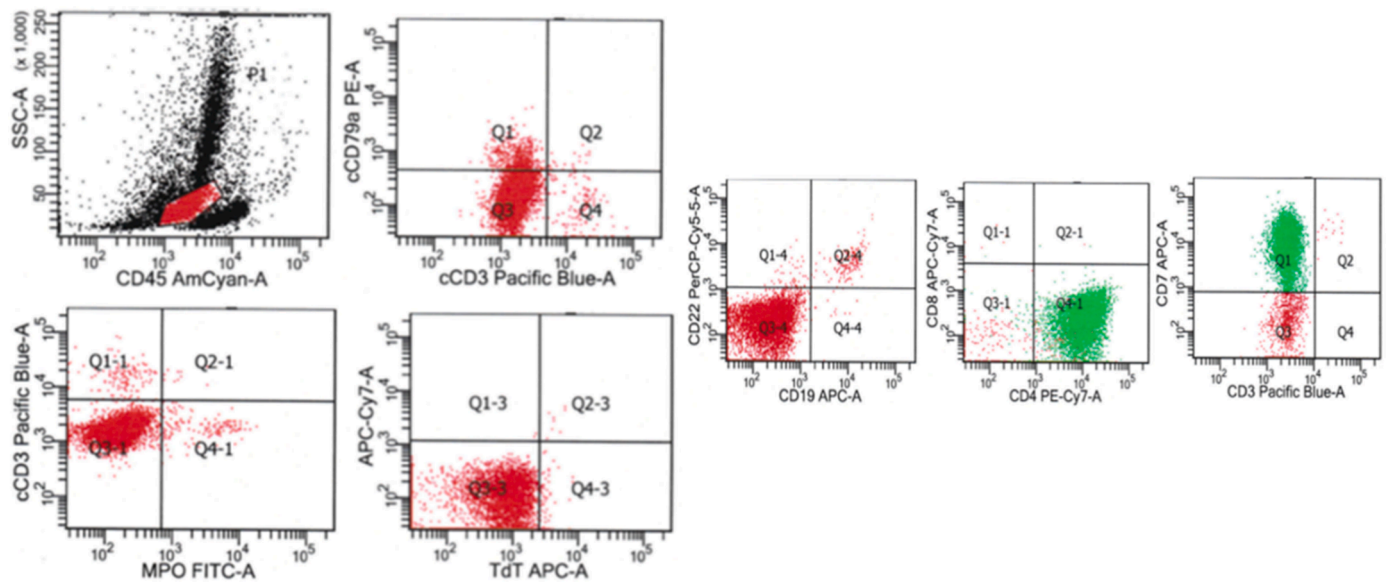


Fig. 2. Screening tube exhibiting negative expression of B, T, myeloid marker and TdT.

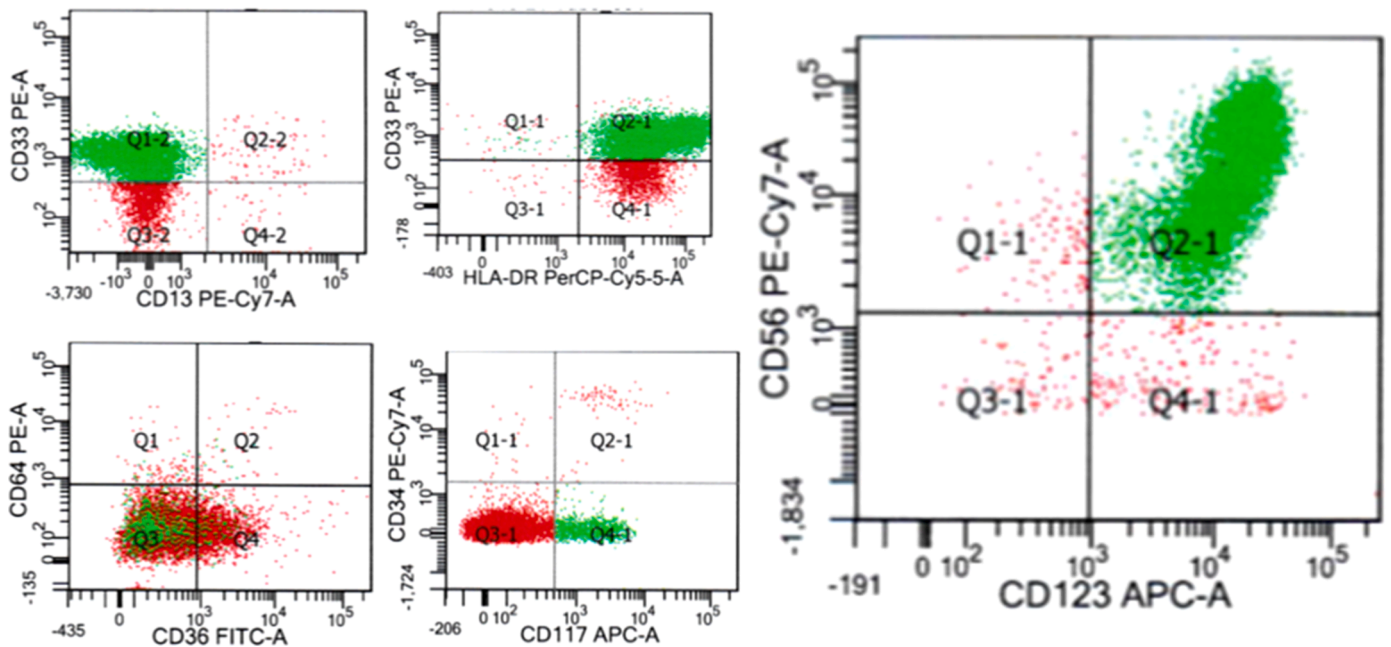


Fig. 3. Extended myeloid panel shows positive CD33 and HLA-DR... pCD specific markers, CD56 and CD123 are positive.

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Informed consent

Written informed consent was taken from patient’s relative.

Detailed author’s contribution

HA took images and drafted manuscript. NS collected data and drafted manuscript. AR conceived the idea, drafted, and critically reviews the manuscript. JLM took images and drafted manuscript. AR conceived the idea, drafted, and critically reviews the manuscript.

Declaration of Competing Interest

None

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