# Blastic plasmacytoid dendritic cell neoplasm: a diagnosis not to be missed, about three case reports

## La leucémie aiguë à cellules plasmacytoïdes dendritiques : un diagnostic à ne pas méconnaître, à propos de trois cas

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### Abstract

**Introduction :** Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a proliferation of plasmacytoid cell precursors. It is a rare and difficult-to-diagnose hematological malignancy with a poor outcome.

**Case presentation:** We report three cases of BPDCN diagnosed in patients of different nationalities (Tunisian, Algerian and Libyan) and varying ages (eight, 65 and 74 years old). Cutaneous involvement was present in all three cases. Cytology was inconclusive in the first case, in favor of acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) in the second and third case respectively. The diagnosis was retained by flow cytometry, highlighting the Cluster of Differentiation (CD) 4 + CD56 + phenotype of the blast population.

**Conclusion:** These observations illustrate diagnosis challenges, the importance of biological/clinical confrontation in order not to misdiagnose this entity. Flow cytometry is an essential diagnostic tool.

**Keyword:** Acute leukemia, cytology, immunophenotyping.

### Résumé

**Introduction :** La leucémie aigüe à cellules plasmacytoïdes dendritiques (LACPD) est une hémopathie maligne caractérisée par une prolifération des précurseurs des cellules plasmacytoïdes. C'est une entité rare, agressive et de diagnostic difficile. Son pronostic est défavorable.

**Observations** : Nous rapportons trois cas de LACPD diagnostiqués chez des patients de nationalités différentes (Tunisienne, Algérienne et Lybienne) d'âges variables (huit, 65 et 74 ans). L'atteinte cutanée était présente dans les trois cas. La cytologie était non concluante dans le premier cas, en faveur d'une leucémie aigue lymphoblastique (LAL) et d'une leucémie aigue myéloblastique (LAM) dans le deuxième et le troisième cas respectivement. Le diagnostic a été retenu par cytométrie en flux en mettant en évidence le phénotype Cluster de Différenciation (CD) 4+ CD56+ de la population blastique.

**Conclusion :** Ces observations illustrent l'intérêt de la confrontation entre clinicien et biologiste pour ne pas méconnaitre cette entité. La cytométrie en flux garde toute sa place pour la confirmation diagnostique.

**Mots clés :** Leucémie aigüe, cytologie, immunophénotypage.

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## INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) was previously called “Blastic NK cell leukemia/lymphoma” or “CD4+/CD56+ keratoderma” or “acute CD4+/CD56+ cell leukemia”(1). It is a rare and aggressive leukemia (<1% of acute leukemia) whose clinical, morphological, and phenotypical features are currently better known (2). However, diagnosis difficulties remain both for the cytologist and the cytometrist. In order not to miss this disease, an extended flow cytometry immunophenotyping panel is needed (3) as well as a clinical/biological confrontation.

Through three cases of BPDCN diagnosed in our flow cytometry laboratory, we describe the diagnostic challenges of this disease. These observations are reported according to the care guidelines (4).

## CASES PRESENTATION

**Case presentation N°1 :** An eight-years-old Algerian child was admitted to the emergency room for persistent fever with multiple ecchymosis and anemia. At admission, the patient was pale and had splenomegaly (two cm from the costal edge), centimeter lymphadenopathy, and multiple sub- centimeter erythematous papules on the face, abdomen, and back (Figure 1). The sedimentation rate was accelerated to 107 mm. The blood count showed hyperleukocytosis with bicytopenia (White Blood Cells (WBC) = 21500 /mm$^3$, Hemoglobin (Hb) = 8 g/dL, Mean corpuscular volume (MCV)= 90 fl, mean corpuscular hemoglobin (MCH) = 28 pg and platelets = 22000 /mm$^3$), neutropenia (215/mm$^3$) and 45 % of blasts at blood smear. The bone marrow was infiltrated by 87% of identical monomorphic difficult-to-classify blasts as in the blood smear. The blasts had medium size with high nucleo-cytoplasmic ratio. The nucleus was regular with fine chromatin inconstantly nucleated.

The cytoplasm was basophilic agranular and inconstantly vacuolated looking like a “Pearls collar” (Figure 1). Bone marrow flow cytometry immunophenotyping confirmed the diagnosis of BPDCN based on the expression of dim Cluster of Differentiation (CD) 45, co-expression of the CD4 and CD56, and the negativity of all myeloid, B, and T lymphoid markers or CD13, CD33, CD117, CD65, CD64, CD15, CD14, CD11c, intra-cytoplasmic myeloperoxidase (MPOc), CD19, intra- cytoplasmic CD79a, CD22, CD10, CD5, CD1a, intra-cytoplasmic, and surface CD3 and CD8. CD2 and CD7 T lymphoid markers were aberrantly expressed. The bone marrow karyotype was normal. The patient had an acute myeloid leukemia (AML) protocol induction with four consolidation cures. Complete cytological remission was achieved.

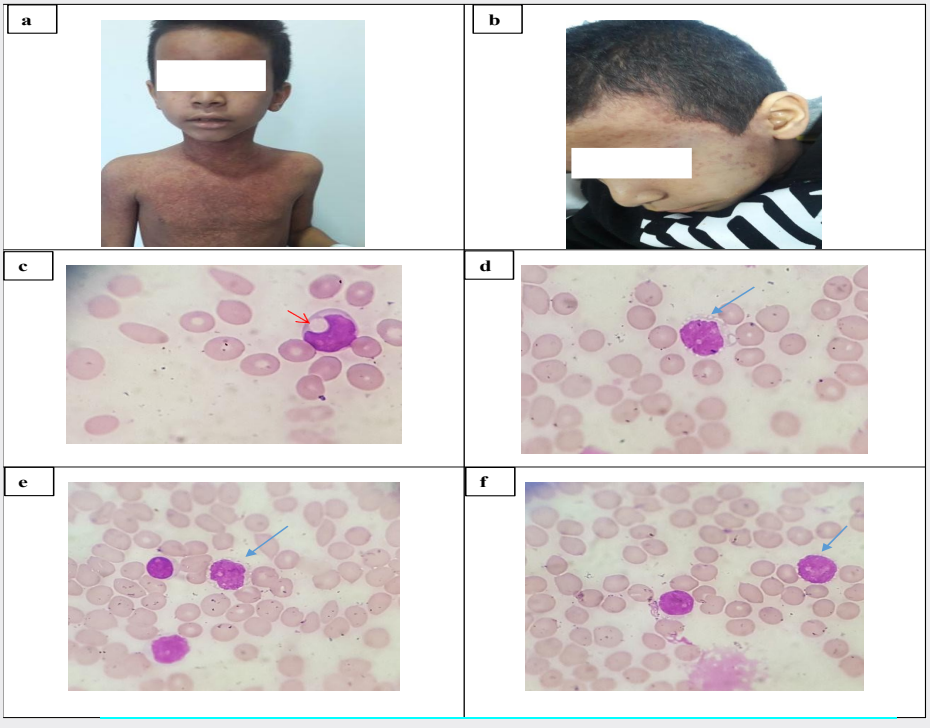


**Figure 1** a, Multiple erythematous subcentimetric papules on the thorax in patient N°1 b. Multiple erythematous subcentimetric papules on the face (especially on the forehead) in patient N°1.

c-f. May-Grunwald-Giemsa stained marrow smear of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN ) at high magnification (patient N°1) showing the presence of blasts with vacuoles (c red arrow) and micro-vacuoles looking like a “pearl collar” at the cytoplasm periphery(d,e,f blue arrow).

**Case presentation N°2 :** A 65-year-old Tunisian man consulted the hematology department for pancytopenia and skin lesions. At admission, the patient was afebrile and had no tumor or hemorrhagic syndrome. Skin examination found ten-days-old multiple macular purpuric non- pruritic ecchymosis of various sizes on the back and trunk. The blood count showed pancytopenia (WBC = 2900 /mm$^3$, Hb = 11 g/dL, MCV = 89 fl, MCH = 27 pg and platelets = 123000 /mm$^3$), neutropenia (783 /mm$^3$) with six per cent difficult-to-classify cells on the blood smear. The myelogram evoked an acute lymphoblastic leukemia (ALL). Bone marrow flow cytometry immunophenotyping confirmed the absence of specific lymphoid B (CD19, intra-cytoplasmic CD79a) and T (intra-cytoplasmic CD3) markers and redressed the diagnosis of CD4+/CD56+BPDCN with CD7 and CD38 aberrant expression (figure 2). CD36 and human leucocyte antigen-D Related (HLA-DR) were also expressed. The cytogenetic study showed hypodiploidy along with a complex karyotype (6q deletion, monosomy 7, 14, 15 and trisomy 12) without breakpoint cluster region- Abelson (BCR – ABL) transcript. Remission was achieved after a corticosteroid therapy.

The patient was included in the clinical trial (sl 401) (5). CD123 was thus tested and was strongly expressed on the blasts. The patient died after seven months of treatment as the result of bone marrow and skin relapse.

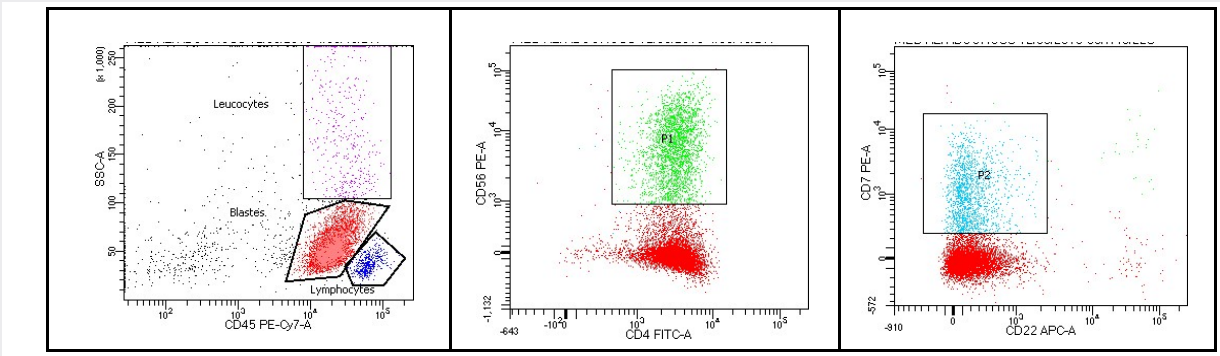


**Figure 2.** Flow cytometry medullar immunophenotyping by flow cytometry (patient N°2) (Cytometer Becton Dickinson Fluorescent Activated Cell Sorter Canto II). CD: Cluster of Differentiation. Markers expression on blasts: CD45+ dim, CD4+, partial expression of CD56 (30%) and partial aberrant expression of CD7 (20%) leading to the diagnosis of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN).

**Case presentation N°3 :** A 74-year-old man from Libya consulted a dermatologist for non-pruritic inconstantly ecchymotic skin infiltrations. The patient had pallor, and multiple diffuse hyperpigmented millimetric papules on the thorax, back, and both upper limbs without tumor or infectious syndrome. Hemostasis and lysis tests were normal. The blood count showed bicytopenia (WBC= 27000 /mm$^3$, Hb= 7 g/dL, VMG= 91 fl, MCH= 27 pg and platelets=30000/mm$^3$) and the blood smear, 30% of blasts. The myelogram evoked an AML. Bone marrow flow cytometry immunophenotyping redressed the diagnosis since blasts were CD34 negative, HLA-DR positive, and CD45 dim with no myeloid marker. In the absence of expression of all the other B and T lymphoid markers, the diagnosis was that of a CD4+/CD56+ BPDCN with aberrant CD7 expression. The bone marrow karyotype was normal. The patient had a single course of chemotherapy (low-dose Aracytine).

## DISCUSSION

These observations illustrate the initial diagnostic challenges of BPDCN, as well as the blast flow cytometry immunophenotyping contribution to the diagnosis confirmation. Both cytological and immunophenotypical diagnosis are not always easy, given the disease's rarity, especially in the Maghreb countries.

The first diagnosis difficulty is cytological. The blasts have a non-specific morphology. Their appearance along with the degree of medullar infiltration varies from one patient to another. Marrow infiltration is more frequent (70% of cases) when the diagnosis is first made by hematologists (6–8) than by dermatologists (9) since isolated skin lesions seem to precede leukemic spread in most cases.

The blasts morphology is pleomorphic. The diameter varies between eight to ten µm, and the nucleocytoplasmic ratio is of approximately 0.6 to 0.8. An elevated ratio gives these cells a lymphoid appearance. The size of the cells is highly variable. When the cells are small with a nucleus, fairly dense or loose chromatin, and sparse cytoplasm, they may mislead to non-Hodgkin's lymphoma (3). The cytoplasm has, in some cases, pseudopod-like cytoplasmic expansions. This aspect, described in ALL as well as in AML, with a monocytic pattern, is again non-specific. The cells have microvacuoles, particularly looking like a "pearl collar" (3) at the cytoplasm periphery, which may mislead the inexperienced cytologist to a rare B-ALL. Signs of mono or multi-lineage myelodysplasia are found in 21% of the patients with (3) and may raise doubts about AML secondary to myelodysplasia.

In our patients, the cytological appearance was that of difficult-to-classify blasts, of ALL or AML blasts, and in only one case, that of the characteristic "pearl collar" look like blasts. Flow cytometry immunophenotyping redressed the diagnosis of BPDCN.

Only immunophenotyping allows for identifying the blast's lineage (Table 1). Positive CD45 confirms their hematopoietic origin. But its expression intensity is dim. Classically, there is no expression of B -CD19, intracytoplasmic CD79a -, T (intracytoplasmic CD3) specific lymphoid or myelomonocytic lineages markers (CD14, CD13, CD3, CD117). CD13, CD33, CD7, CD2 and CD38 markers could be aberrantly expressed (1). These markers alone are insufficient to assign a myeloid or lymphoid T-cell to a lineage. It's the co-expression of CD4+ and CD56+ that confirms the diagnosis. It should be sought in the reference panels.

**Table 1.** Summary of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) markers.

| Markers | BPDCN cells |
|---|---|
| ***T markers*** | |
| *CD2* | *+/-* |
| CD3 | - |
| **CD4** | **+** |
| CD5 | - |
| *CD7* | *+/-* |
| CD8 | - |
| **Myelo-monocyte markers** | |
| CD13 | - |
| CD14 | - |
| *CD33* | *+/-* |
| **CD36** | **+** |
| ***NK markers*** | |
| CD16 | - |
| **CD56** | **+** |
| **CD57** | **+** |
| ***Cytokine receptors*** | |
| CD116 | **+/-** |
| **CD123** | **++** |
| ***Dendritic cell markers and co-stimulatory molecules*** | |
| CD1a | **-** |
| CD11c | **-** |
| CD83 | **+/-** |
| **HLA classe I** | **+** |
| **HLA-DR** | **+** |
| CD40 | **+/-** |
| CD80 | **+/-** |
| CD86 | **+/-** |
| **B DCA-2** | **+** |
| **B DCA-4** | **+** |
| B DCA-3 | **-** |
| B DCA-1 | **-** |
| ***Markers of hematopoietic progenitors*** | |
| **CD38** | **+** |
| CD34 | **-** |
| ***Panleukocytes markers*** | |
| **CD45-RA** | **+** |
| CD45-RO | **-** |
| **IL3** | **+** |

BDCA: Blood dendritic cell antigen, CD: Cluster of Differentiation, HLA: human leucocyte antigen, HLA -DR: human leucocyte antigen- DRelated, IL3 : Interleukin 3.

The second diagnosis difficulty is immunophenotypic, when CD56 is not expressed. There are reported cases of BPDCN that do not express CD56 (10,11). This acute leukemia may be missclassified as undifferentiated acute leukemia, since dendritic cell markers such as CD303, Blood dendritic cell antigens (BDCA2) are only tested in a few specialized centers.

In a study of 22 cases of BPDCN, Tsagarakis et al. (12) concluded that BPDCN can be safely diagnosed by flow cytometry in the presence a hypo-granularity, dim CD45+, CD4+/ CD56+ co-expression, HLA-DR+ and high CD123+.

In our patients, the blasts expressed dim CD45 and a co-expression CD4 and CD56. In two patients, it was believed that T lymphoid markers (CD2 and CD7) were aberrantly expressed, after exclusion of the diagnosis of T-ALL on the basis of the negativity of intra-cytoplasmic CD3. Since the CD123 marker is not available in our laboratory, it was tested in only one patient as part of his inclusion in a clinical trial and was positive.

These observations illustrate the importance, in case of suspicion of acute leukemia with a not evocative or difficult to classify or even conclusive cytology, to always complete by immunophenotyping and to look for the co-expression of CD4 and CD56. A comparison with other clinical and biological features, including skin lesions and cytopenia, is also necessary.

## CONCLUSION

In spite of immunophenotypic progress, the diagnosis of BPDCN remains constraining for cytometry laboratories when they don't have a sufficiently exhaustive immunophenotyping panel, especially in the presence of inconclusive cytology. The clinical/biological confrontation is necessary in order not to misdiagnose this disease with a poor prognosis. The clinical research results are still to be discovered.

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