

CASE REPORT

A Case of Plasmacytoid Dendritic Cell Leukemia

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Introduction: Plasmacytoid dendritic cell leukemia is a rare subtype of acute leukemia, which has recently been established as a distinct pathologic entity that typically follows a highly aggressive clinical course in adults. The aim of this report is to present a case of plasmacytoid dendritic cell leukemia due to its rarity and difficulty to recognize and diagnose it.

Case report: We present a case of a 67 year-old man who presented multiple subcutaneous lesions on his face, neck, chest and upper extremities with reddish-brown, brown colour. In the bone marrow aspirate 83% of the blast cells were found. Immunophenotypically the blasts were positive for CD4, CD56, CD123 (high intensity), CD36, CD22, CD10 (10.42%), CD33, HLA-DR, CD7 (9.24%), CD38 (34.8%) and negative for CD13, CD64, CD14, CD16, CD15, CD11b, CD11c, CD3, CD5, CD2, CD8, CD19, CD20, CD34. The skin biopsy showed lymphohistiocytoid infiltration in the dermis. The patient was diagnosed with acute plasmacytoid dendritic cell leukemia and received polychemo-therapy with rapid response of skin lesions and blastic infiltration of the bone marrow. After 3 courses of polychemotherapy the cutaneous lesions reappeared and multiplied. The blast infiltration in the bone marrow increased to 70%. A more aggressive polychemotherapy regimen was administered, but the patient presented serious complications (febrile neutropenia) and died in septic shock 8 months after the initiation of treatment.

Conclusions: Immunophenotyping of blasts cells is indispensable in the diagnosis of plasmacytoid dendritic cell leukemia. The CD4+, CD56+, lin-, CD123 ++high, CD11c-, CD36+, HLA-DR+, CD34-, CD45+ low profile is highly suggestive for pDCL. The outcome of plasmacytoid dendritic cell leukemia is poor. Despite the high rate of initial response to treatment, early relapses occur and the patients die of disease progression.

Keywords: plasmacytoid dendritic cell leukemia, CD4+/CD56+/lin- neoplasm, immunophenotyping, CD123

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Introduction

Plasmacytoid dendritic cell leukemia (pDCL) is a rare subtype of acute leukemia that has recently been established as a distinct pathologic entity [1]. Due to the uncertain histogenesis of this neoplasm, the name of this entity was changed several times: agranular CD4+ NK-cell leukemia, blastic NK-cell leukemia/lymphoma, agranular CD4+/CD56+ hematodermic neoplasm [2]. Lucio et al. suggested the plasmacytoid dendritic cell origin for this neoplasm [3]. In 2005 it was classified by the WHO-EORTC (World Health Organization/European Organization for Research and Treatment of Cancer) classification for cutaneous lymphomas as CD4+/CD56+ hematodermic neoplasm or early plasmacytoid dendritic cell leukemia/lymphoma [4]. In 2008 the WHO introduced the term blastic plasmacytoid dendritic cell neoplasm (BPDCN) or plasmacytoid dendritic cell leukemia [1]. Plasmacytoid dendritic cells serve as a principal source of type I interferon and are involved in a wide variety of immune functions: antiviral, antitumoral immunity, peripheral tolerance [5].

BPDCN predominantly affects older adults, but pediatric cases were also described [6]. The male/female ratio is 3.5/1, the median age at diagnosis is 57.5/66.4 years, being lower in the case of females [7].

The clinical features of BPDCN are in the majority of cases cutaneous involvement with subsequent or simultaneous extension to bone marrow and peripheral blood. The disease may affect other areas: lymph node, spleen, liver, central nervous system, tonsils, lung [8]. A minority of the cases present with fulminant leukemia and lack of skin manifestations [9]. Tumor cells show an immature, blastic appearance with a greater variability of morphologic features [10]. The histopathological analysis of cutaneous lesions shows a mononuclear cell infiltration into the dermis without angiotropism that does not damage the vessels and spares the epidermis [11].

The diagnosis of pDCL is based on the immunophenotype of the tumor cells: CD4+, CD56+, lineage negative (intracytoplasmic MPO-, CD3-, CD79a-), CD11c-, CD116 low, CD123 ++high, CD36+, HLA-DR+, CD34, CD45 low [12]. Despite the apparently indolent clinical presentation and initially good response to the multiagent chemotherapy, relapses are frequent, with an aggressive clinical course. The prognosis is poor with a median survival of 12–14 months [7,9,13]. At present, there is no consensus regarding the optimal treatment of pDCL [14], long term survival can be obtained only with allogeneic stem cell transplantation during the first remission [13,15].

The aim of this report is to present a case of plasmacytoid dendritic cell leukemia, due to its rarity and difficulty to recognize and diagnose it.



Fig. 1. Multiple cutaneous infiltrations on the face and trunk at time of diagnosis

Case report

A 67-year old man presented in our Clinic with multiple cutaneous lesions on his face, neck, back, chest and upper extremities with reddish-brown and brown colour (Figure 1). Upon physical examination there was no lymphadenopathy or hepatosplenomegaly.

The patient had associated diseases: chronic ischemic cardiopathy, atrial fibrillation, left ventricular aneurysm, NYHA III class heart failure and permanent pace-maker for AV-block. The routine laboratory tests, including biochemistry, liver function, renal function were within normal range, except an elevated lactate dehydrogenase value of 647 U/l. The blood count showed normal white blood cell count, anemia and thrombocytopenia: WBC: $6.19 \times 10^9/l$, Hgb: 11.6 g/dl, Plt: $63 \times 10^9/l$. The peripheral blood smear showed 14% blasts and the bone marrow smear 83% blasts. Morphologically the blast cells were pleomorphic with heterogeneous size. The nuclei were round, irregular or indented, the nucleoli were visible. The cytoplasm was slightly basophilic, non-granular, with heterogeneous structure, presenting vacuoles or pseudopodia-like membrane expansion (Figure 2).

Skin biopsy demonstrated lymphohistiocytoid infiltrate involving the dermis and subcutis, without angiotropism, but sparing the epidermis. Immunophenotyping by flow-cytometry was performed. The blasts were positive for CD4, CD56, CD123 (high), CD36, HLA-DR, CD33, CD22, CD10 (10.42%), CD7 (9.24%), CD3 (34.8%) (Figure 3) and were lineage negative (intracytoplasmic MPO, CD3, CD79a), and negative for the following tested surface markers: CD64, CD14, CD16, CD13, CD15, CD11b, CD11c, CD3, CD5, CD2, CD8, CD19, CD20, CD34. The final diagnosis was plasmacytoid dendritic cell leukemia.

Given the associated cardiac diseases and permanent pace-maker, the patient was treated with a less aggressive

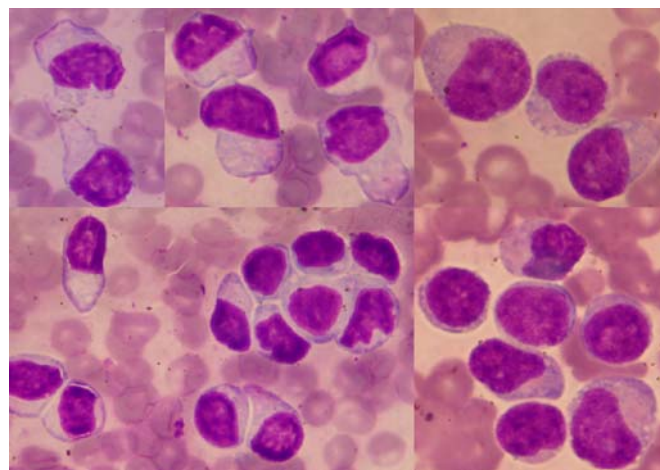


Fig. 2. Morphology of the blasts. Size of blasts: heterogeneous; Nucleus: round, irregular or indented; Nucleoli: visible; Cytoplasmic vacuoles, pseudopodia-like membrane expansions

sive polychemotherapy (PCT) with Vincristine, Alkeran, Methylprednisolonum. For thrombocytopenia we used supportive treatment with platelet transfusion. The patient obtained a rapid response of the skin lesions, in the peripheral blood there were no blasts and the tumor cell infiltration decreased in the bone marrow to 10%. After the PCT the patient developed complications: prolonged febrile neutropenia and thrombocytopenia (WBC: $0.7 \times 10^9/l$, Hgb: 9.9 g/dl, Plt: $41 \times 10^9/l$) which was treated with granulocyte colony stimulating factor (G-CSF), antibiotics and platelet transfusion. After 3 courses of PCT the cutaneous lesions reappeared and multiplied. WBC: $4.83 \times 10^9/l$, Hgb: 12.8 g/dl, Plt: $23 \times 10^9/l$. The blast infiltration in the bone marrow increased to 70%. We administered a more aggressive PCT regimen, 2 courses with Methotrexate and CHOP (Cyclophosphamide, Hydroxidaunorubicine, Vincristine, Prednisone) without anthra-

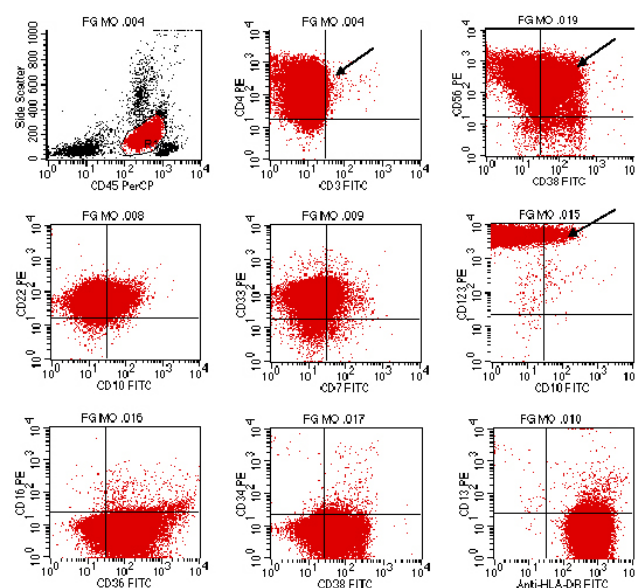


Fig. 3. The blasts are positive for: CD4+, CD56+, CD123+++, CD36+, CD33+, CD22+, CD10+ (10.42%), CD7+ (9.24%), CD38+ (34.8%)

cycline, adapted to the cardiac disease of the patient. But the patient had serious complications: febrile neutropenia and he died in septic shock 8 months after the initiation of PCT.

Discussion

Plasmacytoid dendritic cell leukemia (pDCL) is a rare entity that comprises less than 1% of all acute leukemias [8], in our laboratory from a total of 237 acute leukemias diagnosed by flowcytometry only 1 was identified as pDCL (0.42%).

pDCL was characterized initially by the co-expression of CD4+ and CD56+ without expression of B-, T-lymphoid, NK-cell or myeloid lineage. However, pDCL can express markers from a different lineage due to aberrant marker expression — a frequent feature of leukemic cells, or due to the fact that dendritic cells can change their morphology, phenotype and functionality depending on their differentiation and/or activation state [16].

The clinical differential diagnosis in this patient included acute myeloblastic or lymphoblastic leukemia with cutaneous infiltrates and NK/T-cell lymphoma. In our patient the blast cells show the immunophenotypic profile described for pDCL: CD4+, CD56+, lin-, CD123 ++high, CD11c-, CD36+, HLA-DR+, CD34-, CD45 low [12], except CD116 that was not determined in our case. The diagnosis of pDCL by flowcytometry can be difficult when blast cells express additional markers and do not fit completely the pDCL profile. The particularity of this case was the presence of other lineage markers: myeloid: CD33, T-lymphoid: CD7, B-lymphoid: CD22, CD10. Some acute myeloblastic and lymphoblastic leukemias may express CD4 and CD56, but other lineage specific markers are used for diagnosis. The EGIL (European Group for the Immunological Characterization of Leukemias) score was < 2 for myeloid lineage and also for lymphoid lineage, so we excluded myeloblastic or lymphoblastic leukemia. This system is based on the number and degree of specificity of the markers (lymphoid and myeloid) expressed by the leukemic cells [17]. Co-expression of CD33, CD2, CD7, CD117, CD22 in pDCL is acceptable and was previously described in several cases [2,16,18]. A number of acute leukemia cases expressed CD123, but pDCL cells express higher levels of CD123 compared to other acute leukemia cells. Nevertheless, the high expression of CD123 is a strong argument in favour of a pDC origin [12].

Mixed myeloblastic/NK-leukemia co-express CD7, CD33 and CD56 marker that correspond to the myeloid and NK-cell precursor. In all reported cases CD4+ and CD36+ were not expressed, but other myeloid markers: CD13, MPO, CD11b were. CD34 was always expressed, which excludes pDCL [2].

NK/T-lymphoma are differentiated by the presence of azurophilic granules in the cytoplasm. Expression of CD56, CD2 can be common in NK/T-lymphoma and pDCL but NK/T-lymphoma do not express CD4 [19]. This type of lymphoma is characterized histopathologically by angio-

tropism and destruction that was not described in our case.

The typical skin lesions, the morphology, the specific immunophenotypic profile of the blast cells facilitate the pDCL diagnosis.

The evolution of the disease was similar as described in literature [7,9,13,14,15]. Despite of a good response to initial treatment, early relapse occurred with aggressive progression of the disease and the patient died 8 months after the initiation of PCT.

Conclusions

Plasmacytoid dendritic cell leukemia (pDCL) is a rare hematological neoplasm.

Immunophenotyping of blasts cells is indispensable in the diagnosis of pDCL. The CD4+, CD56+, lin-, CD123++ high, CD11c-, CD36+, HLA-DR+, CD34-, CD45 low profile is highly suggestive for pDCL.

The outcome of pDCL is poor. Despite the high rate of initial response to treatment, early relapse occurs and the patients die of disease progression.

For older patients the optimal approach for pDCL therapy is unknown. Thus, it is important to elucidate the origin of the neoplastic cells for determination of the appropriate therapy.

References

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th Edition. Bosman FT, Jaffe ES, Lakhani SR, Ohgaki H. Lyon, France: International Agency for Research on Cancer. 2008.
2. Garnache-Ottou F, Feuillard J, Saas P. Plasmacytoid dendritic cell leukaemia/lymphoma: towards a well defined entity? *Br J Haematol* 2007; 136:539-548.
3. Lúcio P, Parreira A, Orfao A. CD123hi dendritic cell lymphoma: an unusual case of non-Hodgkin lymphoma. *Ann Intern Med*. 1999;131:549-550.
4. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005;105:3768-3785.
5. Charles J, Chaperot L, Salameire D, et al. Plasmacytoid dendritic cells and dermatological disorders: focus on their role in autoimmunity and cancer. *Eur J Dermatol*. 2010;20(1):16-23.
6. Jegalian AG, Buxbaum NP, Facchetti F, et al. Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic feature and clinical presentations. *Haematologica*. 2010;95(11):1873-1879.
7. Facchetti F, Ungari M, Marocolo D, Lonardi S, Vermi W. Blastic plasmacytoid dendritic cell neoplasm. *Hematology Meeting Reports*. 2009;3(3):1-3.
8. Jacob MC, Chaperot L, Mossuz P, et al. CD4+ CD56+ lineage negative malignancies: a new entity developed from malignant early plasmacytoid dendritic cells. *Haematologica*. 2003;88(8):941-955.
9. Rauh MJ, Rahman F, Good D, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation, lacking cutaneous involvement: Case series and literature review. *Leuk Res*. 2012;36:81-86.
10. Cota C, Vale E, Viana I, et al. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm-morphologic and phenotypic variability in a series of 33 patients. *Am J Surg Pathol*. 2010;34(1):75-87.
11. Petrella T, Bagot M, Willemze R, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol*. 2005;123:662-675.
12. Garnache-Ottou F, Feuillard J, Ferrand C, et al. GOELAMS and GEIL study - Extended diagnostic criteria for plasmacytoid dendritic cell leukaemia. *Br J Haematol*. 2009;145:624-636.
13. Reimer P, Rüdiger T, Kraemer D, et al. What is CD4+CD56+ malignancy and how should it be treated? *Bone Marrow Transplant*. 2003;32:637-646.
14. Feuillard J, Jacob MC, Valensi F, et al. Clinical and biologic features of CD4(+)CD56(+) malignancies. *Blood*. 2002;99:1556-1563.

15. Dietrich S, Andrulis M, Hegenbart U, et al. Blastic plasmacytoid dendritic cell neoplasia (BPDC) in elderly patients: results of a treatment algorithm employing allogeneic stem cell transplantation with moderately reduced conditioning intensity. *Biol Blood Marrow Transplant.* 2011;17:1250-1254.
16. Bueno C, Almeida J, Lucio P, et al. Incidence and characteristics of CD4(+)/HLA DRhi dendritic cell malignancies. *Haematologica.* 2004;89(1):58-69.
17. Béné MC. Biphenotypic, bilineal, ambiguous or mixed lineage: strange leukemias! *Haematologica.* 2009;94(7):891-893.
18. Reineks EZ, Osei ES, Rosenberg A, Auletta J, Meyerson HJ. CD22 expression on blastic plasmacytoid dendritic cell neoplasms and reactivity of anti-CD22 antibodies to peripheral blood dendritic cells. *Cytometry B Clin Cytom.* 2009;76(4):237-248.
19. Suzuki R, Suzumiya J, Yamaguchi M, et al. NK-cell Tumor Study Group - Prognostic factors for mature natural killer (NK) cell neoplasms: aggressive NK cell leukemia and extranodal NK cell lymphoma, nasal type. *Ann Oncol.* 2010;21(5):1032-40.