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Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Case Report

Morphological evidence of leukemic plasmacytoid dendritic cells in a case of acute myeloid leukemia with pDC and monocytic differentiation

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Abstract

The role of plasmacytoid dendritic cell (pDC) proliferation in acute myeloid leukemia (AML) is less understood. There are two polar pDC neoplasms recognized by World Health Organization (WHO) currently, including blastic plasmacytoid dendritic cell neoplasm, and mature plasmacytoid dendritic cell proliferation in myeloid neoplasms. Morphologically, AMLs showing a gamut of pDCs ranging from blastic to immature pDCs, to more mature forms, fall outside the literal purview of these two entities. With genetic studies proving that pDCs in such cases share the same mutational profile as leukemic blasts, they may be more aptly designated as AML with pDC differentiation (pDC-AML). Flow cytometry is required to demonstrate pDC-AML, and their clonality is established by genetic studies. However, it is difficult to prove their leukemic nature on morphology. We present a case of pDC-AML with pDCs showing presence of Auer rods. To the best of our knowledge this is the first case with morphological evidence of leukemic pDCs.

Keywords: Acute myeloid leukemia, pDC differentiation, Auer rods, flow cytometry, RUNX1.

Received: 05-12-2024; **Accepted:** 27-02-2025; **Available Online**: 15-03-2025

1. Introduction

Plasmacytoid dendritic cells (pDCs) are hematopoietic cells produced in the bone marrow, usually accounting for <01% of nucleated cells in peripheral blood and bone marrow.[1,2] They have immune-modulatory functions - producing type 1 interferon, and also serve as antigen presenting cells.[3,4] pDCs may be anti-tumorogenic - based on the nature of IFN-α produced, or pro-tumorogenic - producing a microenvironment conducive to regulatory T-cells.[2] The cell-of-origin of normal pDCs has been controversial, conflicting between common myeloid, macrophage DC, and lymphoid progenitors.[5-8] pDC malignancies are thought to arise from myeloid progenitors, as evidenced by their association with myeloid neoplasms.[7-9] WHO, in its latest edition (5th ed., 2022) lists two pDC-related malignancies: *blastic plasmacytoid dendritic cell neoplasm (BPDCN)*, and *mature pDC proliferation (MPDCP) associated with myeloid neoplasms (MPDMN)*, the latter including acute myeloid leukemia (AML).[9] However, some authors propose recognizing AML with pDC differentiation (pDC-AML) as a distinct entity.[4,8,10,11] This is supported by flow cytometry which demonstrates maturation of blasts towards immature, and maturing pDCs, as well as genetics that helps establish identical clonal aberrations in these cell populations. While microscopy alone is challenging to diagnose pDC-AML, when discernible, pDCs in various stages of maturation are seen. We report a case of pDC-AML showing florid pDC proliferation, and morphological proof of leukemic pDCs, bearing cytoplasmic Auer rods (**Figure 1A-C**). The latter is concurrent with myeloid origin of these neoplasms.

2. Case Report

A 57-year-old female, known case of type 2 diabetes mellitus, on routine checkup was found to have pancytopenia. On ultrasound abdomen-pelvis, there was moderate splenomegaly and mild hepatomegaly. Peripheral blood smear examination (PBSE) revealed dimorphic anemia with dyspoietic myeloid cells, and thrombocytopenia. Bone

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https://doi.org/10.18231/j.ijpo.2025.022

marrow microscopy revealed a hypercellular marrow with low blasts (<05%) and tri-lineage dysplasia. Differential diagnoses considered were myelodysplastic neoplasm (MDS) and myelodysplastic/myeloproliferative neoplasm (MDS/MPN; in view of splenomegaly). Conventional karyotyping (CK) analysis showed gain of chromosome 8 in one metaphase and loss of chromosome 20 in all analysed metaphases along with three small marker chromosomes (47-48,XX,-20,+mar1,+mar2+mar3[12]/49,XX,+8,-20,+mar1, +mar2,+mar3[1] ISCN 2020). Next generation sequencing (NGS) found clinically relevant mutations in RUNX1 [variant allele frequency (VAF) -10.47%] and CBL (VAF-25.12%) with PDCG1 deletion (CNV–23.36 kb). She was initiated on oral Danazol, 200 mg., once daily.

Seven-months-later, her PBSE showed a leucoerythroblastic blood picture with increased blasts (~18%) and monocytosis. Bone marrow examination confirmed transformation to AML with ~32% blasts and monocytosis. There was also a prominent population of pDCs in various stages of maturation, many of them showing presence of Auer rods (**Figure 1A-C**). Flow cytometry (FCM) features were consistent with AML showing pDC and monocytic differentiation (**Figure 2**). BM biopsy immunohistochemistry showed interstitially scattered CD123-positive cells, composed of blasts intermixed with pDCs and monocytes, which were difficult to distinguish from one another (**Figure 1D-F**). CK, at this point, revealed consistent loss of chromosome 20 in all metaphases and gain of 02-03 chromatin fragments (47-48, XX,-20,+mar1,+mar2,+mar3[cp-10] ISCN 2020). She was started on intravenous Decitabine, 100 mg. Twelve days later, she succumbed to her illness.

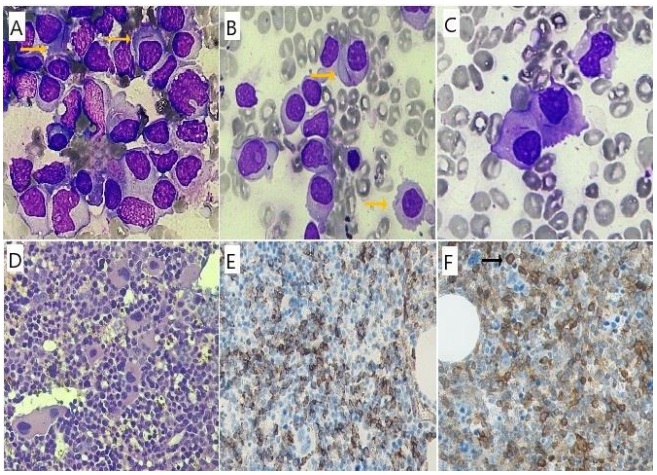

Figure 1: Bone marrow showing increase in blasts with pDC differentiation. (**A-C**): Bone marrow aspirate (x1000, Giemsa stain) shows blasts and pDCs in various stages of maturation, many pDCs exhibit Auer rods (**yellow arrow**). (**D**): Bone marrow biopsy (x400, H & E stain) shows interstitial increase in blasts, and dysmegakaryopoiesis. (**E**): CD34 IHC (x400) highlights increase in blasts. (F) On CD123 IHC (x400), it is difficult to differentiate blasts from pDCs; however, few discernible pDCs with more intense staining (black arrow) are noted

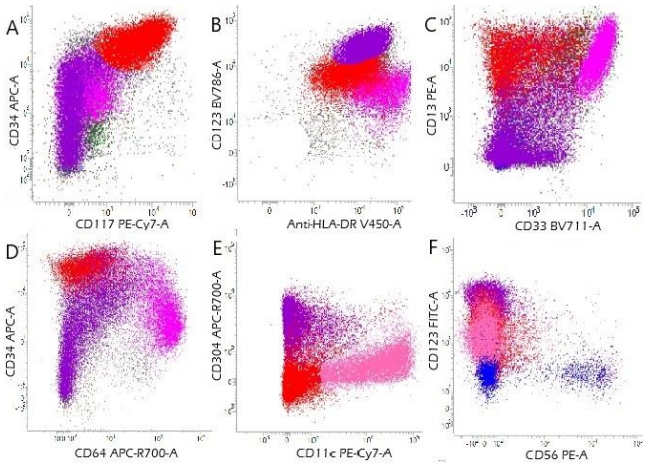

Figure 2: Flow cytometry showing AML with pDC and monocytic differentiation. (**A**): Abnormal myeloid blasts (red) are identified; CD34 expression is also noted in pDCs (purple) in a moderate, heterogeneous pattern, and in monocytes (pink) at a dimmer level. (**B**): CD123 is brightest in pDCs, and HLA-DR is brightest in monocytic cells. (**C**): While monocytes show normal expressions of CD13 and CD33, there is loss of CD33 in blasts and dim CD33 in a subset of pDCs. (**D & E**): Blasts are seen acquiring monocytic – CD64 and CD11c, and pDCs maturity markers - CD304. (**F**): All three populations are negative for CD56

3. Discussion

BPDCN, MPDMN, and the proposed pDC-AML are morphologically, immunophenotypically, and genetically distinct.[2,4,8] BPDCN comprises of proliferation of blastic pDCs. In BPDCN, leukemic cells are derived from the CD56-positive subset of pDC precursors, while in pDC-AML, they are believed to originate from CD34-positive blasts.[8] MPDMN show mature pDCs with moderate amphophilic cytoplasm, cytoplasmic pseudopodia, eccentric nuclei, and clumped chromatin. pDC-AML shows a range of pDCs in various stages of maturation, including blastic precursors, interim forms and mature pDCs. In bone marrow biopsy, tight nodular aggregates of mature pDCs are commonly seen in MPDMN. In contrast, there is an interstitial distribution of pDCs in pDC-AML, which rarely may form loose aggregates.[8] Neoplastic pDCs are positive for CD303, CD304, CD123, TCF4, and usually negative for TCL1, CD34, TdT, and CD56 on immunohistochemistry.[4,8]

pDC-AML is defined as AML with >02% pDCs by FCM, accounting for 03-05% of all AMLs.[2,8] However, the precise incidence is difficult to assess in view of its rarity, and subjective interpretation on morphology. They usually occur in elderly (>60 years) with a male preponderance, and less frequent skin involvement than BPDCN.[4,7]

On FCM, normal pDCs account for 0.24-0.25% of nucleated cells.[7] They are brightly positive for CD123 and

HLA-DR, showing a maturation pattern involving three stages with progressive loss of CD34 and CD117, and gradual acquisition of CD4, CD36, CD303, and CD304.[4,8,12] In pDC-AML, blasts mature towards pDCs, and commonly monocytes.[7] Blasts generally express CD34, HLA-DR, and CD123 (dimmer than pDCs) with myeloid lineage markers such as CD117, CD13, CD33, and variable TdT, CD4, CD7, CD5, CD22, and MPO. Neoplastic pDCs express bright CD303 (higher than in BPDCN), CD123 (lower than in BPDCN), CD304, HLA-DR, with lower expression or absence of TCL1, and are usually negative for CD56 (similar to normal pDCs).[2,4,7,8] They show heterogeneous CD34 (lower than coexistent myeloblasts) and may express lymphoid markers such as CD22, CD4 (less frequent than BPDCN), CD7, and CD5.[4,7] Other markers often expressed include CD38, CD36, CD33, CD25, CD71, CD117 in heterogeneous patterns. Less common markers include CD13, CD2, CD5, CD64.[4,8] They are negative for CD14, CD15, CD19, MPO.[7,8] Our case showed abnormal myeloid blasts maturing independently toward monocytes and pDCs, with pDCs expressing heterogeneous CD34, bright CD123 and CD304 (**Figure 2A-F**).

MPDMN is most often seen in chronic myelomonocytic leukemia (CMML), and pDC-AML is commonly associated with monocytic differentiation.[7] Studies have proved that pDCs and monocytes in these respective cases originate from, have the same genetic anomalies as blasts, with similar VAF in these cell populations.[1,2,7,8,13] It is largely unclear if CMML and AML associated with MPDCP share common pathogenic mechanisms.[9] Some authors have shown that CMML is associated with a high risk of transformation to AML, and pDCs have the same genetic aberrations as CMML clones.[1]

A number of cytogenetic and molecular abnormalities have been described in pDC-AML, with RUNX1 mutation being the most common, seen in 64-73% cases.[2,7,8] Mutation in RUNX1 causes exasperation of interferon-associated pDC transcription programs, and may cause a RUNX2 switch.[2,13,14] RUNX2, critical for pDC differentiation, eventually may lead to pDC-AML. RUNX1 mutation occurs frequently with other mutations in pDC-AML, most commonly ASXL1 and DNMT3A and TET2. Other known mutations include, FLT3-ITD, EZH2, NRAS ZRSR2, SRSF2, SF3B1, CBL. Cytogenetic abnormalities include monosomy 7, trisomy 8, trisomy 13, del(5q), KMT2A rearrangement and EZH2 deletion (FISH).[7] CBL mutations commonly arise in MDS/MPN, being associated with a high-risk to transform to AML.[15] With our case showing RUNX1 as well as CBL mutations, it seems probable that pDC-AML arose from an underlying MDS/MPN – likely CMML.

pDC-AML is associated with poor prognosis, remission failure, and frequent relapse.[2,8,11] However, anti-CD123 therapy such as tagraxofusp, IMGN632, and CD123 CAR T-cells, have shown to reduce pDC and blast burdens.[2,16-19] They have become a frontline therapy for BPDCN, and would be of practical benefit in pDC-AML, serving as a bridge therapy for transplantation.[11]

4. Conclusion

The present case places emphasis on considering pDC-AML as a distinct neoplasm. As most cases may not show obvious pDC differentiation on morphology, they are often indistinguishable from other AMLs. This, is addition to there being no genetic abnormality specific/exclusive to pDC-AML at present, makes flow cytometry analysis invaluable in establishing the diagnosis. With concurrent anti-CD123 targeted therapy, this acute leukemia, albeit considered high-risk, may show better response and improved overall survival.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Ray M, Naik MV, Ross RC. Morphological evidence of leukemic plasmacytoid dendritic cells in a case of acute myeloid leukemia with pDC and monocytic differentiation.. *Indian J Pathol Oncol*. 2025;12(1):97–100.