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Blastic Plasmacytoid Dendritic Cell Neoplasm, a Very Rare Hematological Malignancy With Initial Cutaneous Involvement: A Case Report

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ABSTRACT
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a very rare and aggressive hematologic malignancy, arising from plasmacytoid dendritic cells (pDCs). BPDCN frequently has, at least initially, exclusively cutaneous presentation.
We present a 45-year-old woman with a 3-month history of rapidly evolving violaceous patches, infiltrated plaques, and bruise-like tumefactions, disseminated on her face and upper trunk. Histopathology of a lesion, along with Flow cytometry of peripheral blood and cerebrospinal fluid, confirmed the diagnosis of BPDCN. The patient received a hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) regimen and six triple intrathecal chemotherapies. Unfortunately, the patient contracted COVID-19 and died of severe respiratory complications, despite all the available treatment modalities.
Our patient presented with typical clinicopathological manifestations of the disease, misdiagnosed for 3 months. The case additionally reflects difficulties in patient management during the COVID-19 pandemic.
Dermatologists should be aware of this rare disease, since the early diagnosis and treatment with new emerging drugs may lead to a better prognosis.

KEY WORDS: blastic plasmacytoid dendritic cell neoplasm (BPDCN), skin, dendritic cells, leukemia, hematologic neoplasm, CD123

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) represents an exceedingly rare, highly invasive hematologic malignancy, arising from plasmacytoid dendritic cells (pDCs), a unique cell type specialized in the rapid production of type I interferons (IFNs), in a response to early stages of viral infection (1). Additionally, these cells have a specific role in immune tolerance, immune regulation, and autoimmunity. Immunophenotypically, normal cells usually express markers such as CD123, BDCA-2 (CD303), and BDCA-4 (CD304) and typically have absent/low expression of CD56 and BCL2 (2). The etiology and pathogenesis of BPDCN are still unknown, but many reports suggest an association with other myeloid malignancies, contributing to the thesis that the perplexing process of genetic mutations and environmental factors could have a pivotal role in the malignant transformation of pDCs (3). Heterogeneous skin lesions, most frequently violaceus nodules and/or macules, are the most common initial presentation of the disease (4). Extra-cutaneous involvement includes lymph nodes, bone marrow, and the liver, but it can also involve other organs such as the lungs and spleen (3). As a consequence of frequent leukemic dissemination of the disease, the prognosis is extremely poor, with a median survival rate of less than two years (5).

Acta Dermatovenerol Croat
2024;32(2):96-101

CASE REPORT

A 45-year-old woman presented with a 3-month history of rapidly growing and painful tumors on her face and upper trunk. One month after the onset of skin lesions, she noticed nasal congestion, pressure in her ears and sinuses, and developed difficulty in swallowing solid food. She was erroneously diagnosed with atypical angioedema and treated with systemic corticosteroids on several occasions, without any significant relief of her symptoms. Before the commencement of the disease, she had been healthy and denied any family history of genetic disorders. Physical examination revealed disseminated violaceous patches, infiltrated plaques, and disseminated bruise-like tumefactions with central ulceration on her face and upper parts of her trunk (Figure 1). Cutaneous manifestations were accompanied by cervical and axillary lymphadenopathy.

Additionally, the patient presented with dyspnea, dysphagia, and epiphora. Although complete blood count (CBC) was normal at the time of initial skin manifestations, after 4 months her CBC showed high leukocytosis (64×10^9/L), thrombocytopenia (87×10^9/L), and anemia (hemoglobin 105 g/L). Besides elevated levels of gamma-glutamyl transferase (GGT) 124 U/L (n. 0-38 U/L), and lactate dehydrogenase (LDH) 1266 IU/L (n. 220-460 IU/L), other biochemical analyses were normal. Chest X-ray examination showed no pathological findings. Ultrasound of soft tissues detected enlarged lymph nodes up to 35 mm in diameter in the cervical, axillary, and inguinal regions. Complete abdominal sonography revealed hepatosplenomegaly. A multislice CT scan of the paranasal sinuses detected pansinusitis. Tumefactions in the patient's nasopharynx and oropharynx were found during rhinolaryngoscopy. Virology tests (HIV Ag/Ab, HBsAg, and anti-HCV Abs) were all negative. Two incisional biopsies of lesions located on the patient's face and upper trunk were performed. Biopsies displayed a dense dermal and hypodermal infiltrate with uniform cells of blastoid morphology and secondary epidermal atrophy without epidermotropism. There was no presence of angioinvasion and coagulative necrosis (Figure 2). Immunohistochemistry (IHC) revealed positivity for CD4, CD43, HLA-DR, and CD123 (Figure 3), but negativity for CD56, MPO, and CD34. Flow cytometry of peripheral blood confirmed

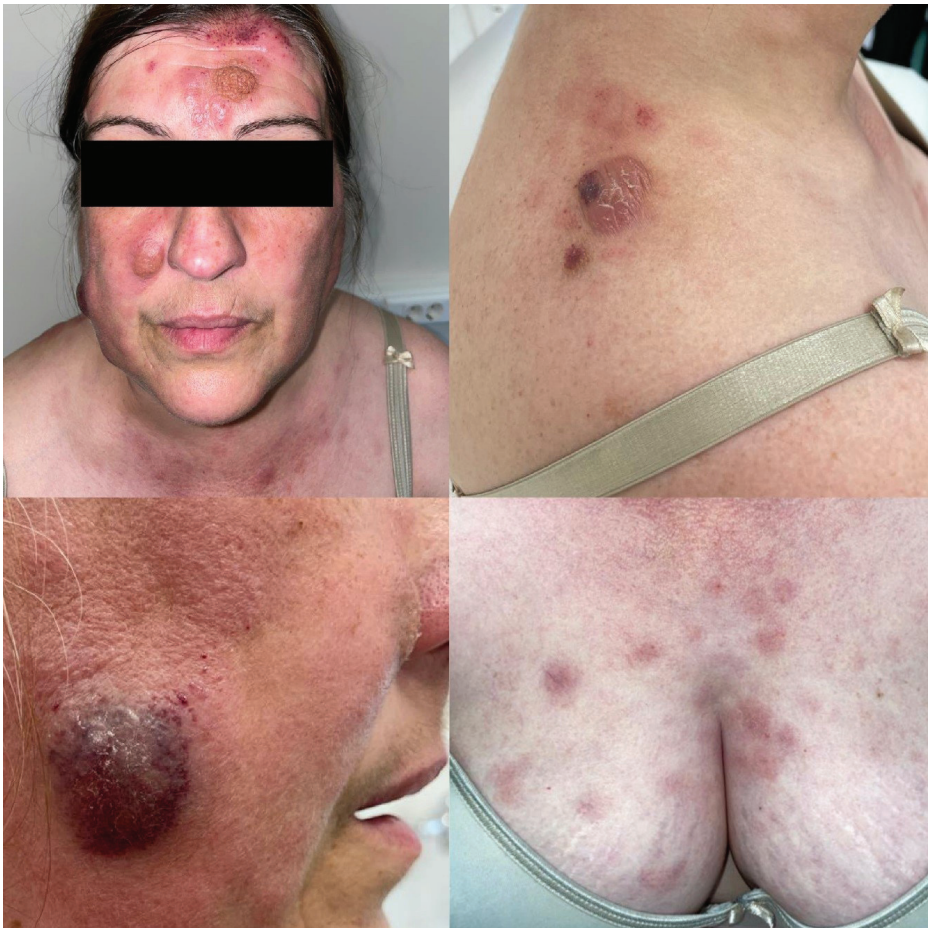

Figure 1. Violaceous patches, infiltrated plaques, and disseminated bruise-like tumors on the face and upper trunk.

Acta Dermatovenerol Croat
2024;32(2):96-101

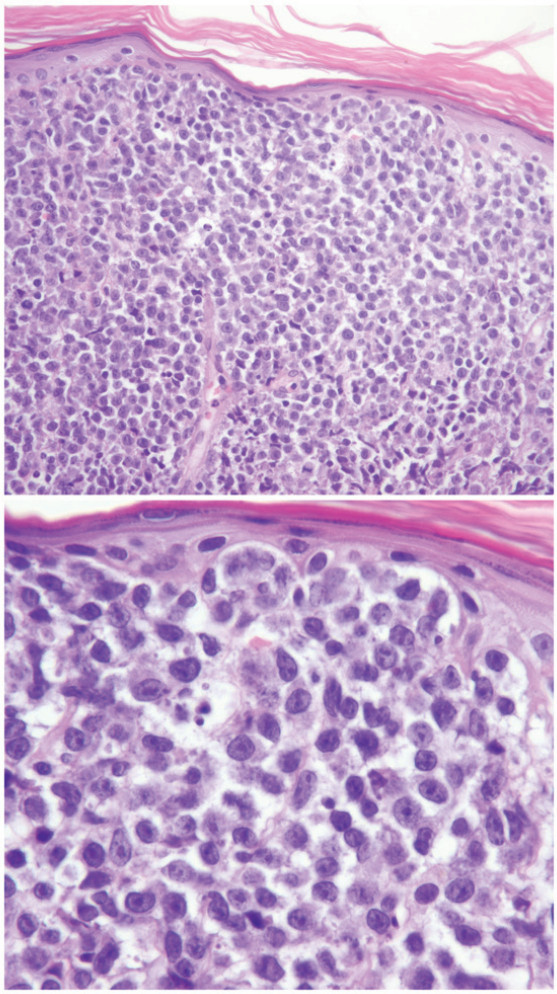

Figure 2. Dense dermal infiltrate consisting of uniform cells of blastoid morphology with sparse basophilic cytoplasm, eccentric, oval nuclei, and loose chromatin with central eosinophilic nucleoli. Secondary atrophy of epidermis, without epidermotropism (hematoxylin and eosin, ×400 and ×1000, respectively).

atypical cells positive for CD45, CD4, CD33, HLA-DR, CD56, and CD123, and negative for other non-linage antigens (CD3, CD14, CD16, CD19, CD20, myeloperoxidase (MPO)), lysozyme, and other specific markers of myeloid, B and T lymphoid, and NK cells. Myelography showed hypercellularity with 60% of large (2-4xLy), atypical blast cells, with round to oval-shaped euchromatic nuclei, one or two nucleoli, and lightly basophilic agranular cytoplasm, lacking cytoplasmic granules and Auer rods. Cytogenetic analysis from the bone marrow revealed a normal female karyotype (46, XX).

Based on clinical, histopathological, and immunophenotype findings, the diagnosis of BPDCN was established. After the diagnostic evaluation, the patient was transferred to the Department of Hematology for further monitoring and treatment. CSF flow cytometry found an immunophenotype similar to the peripheral blood ($CD45^+$, $HLA\text{-}DR^+$, $CD123^+$, $CD43^+$, $CD7^+$, $CD4^+$). The patient received a hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), along with six triple intrathecal chemotherapies (cytarabine, methotrexate, and methylprednisolone). Prolonged agranulocytosis was detected during the first cycle of hyper-CVAD therapy, and immediate treatment with granulocyte growth factor (G-CSF) was provided. A partial remission with 6% of bone marrow blast cells was achieved. The patient had not received a COVID-19 vaccine, and unfortunately, after the second hyper-CVAD cycle, the patient's hospital course was complicated by COVID-19 infection. 35 days after the diagnosis of COVID-19, the patient died due to respiratory failure and cardiac arrest, despite all the available therapy.

DISCUSSION AND CONCLUSION

Until recently, blastic plasmacytoid dendritic cell neoplasm (BPDCN) has undergone frequent changes in nomenclature due to the lack of well-defined diagnostic criteria and insufficient knowledge regarding the precursor cells. BPDCN was previously known as natural killer (NK) cell leukemia/lymphoma. In 2016, after additional discoveries, the World Health Organization (WHO), in collaboration with the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP), reclassified BPDCN as an autonomous entity in the group of myeloproliferative neoplasms (6).

The estimated annual incidence does not exceed 0.44 per 100,000 population (5). The disease may be underreported due to the lack of standardized diagnostic criteria and limited awareness of the disease among healthcare providers (5). The Surveillance

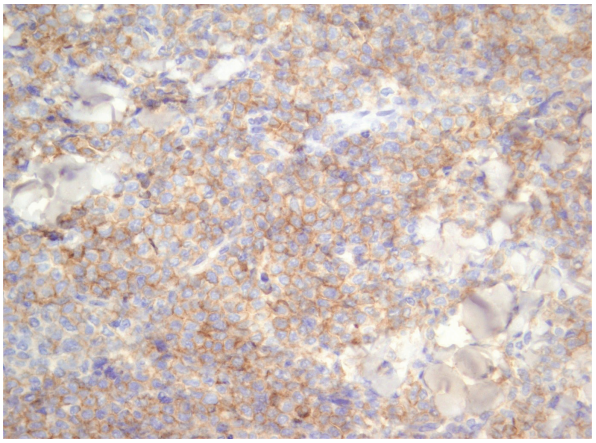

Figure 3. Immunohistochemistry staining: pronounced membrane positivity for CD123.

Acta Dermatovenerol Croat
2024;32(2):96-101

Epidemiology and End Results (SEER) data indicate that BPDCN generally exhibits a predominance in men, but it can also affect women, as in the case of our patient. Although the disease mostly affects elderly people, it can occur in individuals of all age groups, as demonstrated in our patient who was diagnosed at the age of 45 years (8). All geographic locations and races are equally affected (7,8). According to the current largest multi-center study summarizing clinical features and outcomes of the disease, almost 90% of patients had polymorphous cutaneous involvement, either localized or widespread. Our patient had cutaneous lesions in the form of nodules and purplish macules and patches, which are found in the majority of BPDCN cases with cutaneous presentation (9). As in 60% of all cases with BPDCN, our patient had bone marrow involvement. Another common manifestation, present in 40% of BPDCN cases, is lymph node involvement, as was the case in our patient. Additionally, our patient also had secondary leukemia, a feature present only in 15% of all cases (9). Our patient had CNS involvement, which is not an uncommon occurrence in this type of cancer. The estimated incidence of CNS involvement, regardless of the presence of symptoms, ranges from 10% to 60%, depending on the study (9,10). The CNS can act as a sanctuary site for cancer cells, evading systemic treatments due, in part, to the blood-brain barrier. This can lead to poorer outcomes and higher risk of disease recurrence (10). The involvement of oral and nasal mucosa, a rare manifestation of BPDCN seen in less than 10% of cases, was observed in our patient. Oral and nasal mucosal involvement can cause pain, discomfort, difficulty in breathing, eating, or speaking, and may lead to a delayed diagnosis as the clinical and histopathological features can mimic other malignancies (11).

Other extra-cutaneous site infiltrations, such as the liver, spleen, lung, breast, kidney, muscle, and heart have been also reported (9). Although our patient had an enlarged liver and spleen, more detailed diagnostic procedures were not carried out due to the rapid progression of the disease.

The appearance and dissemination of cutaneous lesions preceding the leukemic phase of the disease is the most common scenario in BPDCN. Presentation with cutaneous lesions or development of skin infiltration after the diagnosis of BPDCN do not influence the final prognosis. Our patient developed leukemic dissemination 4 months after the initial cutaneous lesions (11,12). Initially, when the skin manifestations appeared, the patient's CBC was normal. However, after 4 months, leukocytosis, anemia, and thrombocytopenia, which are the most common laboratory abnormalities in BPDCN, were detected (12).

Prompt diagnosis is based on clinical findings and must be confirmed by histopathology and immunophenotyping. Our patient's histopathological findings were consistent with BPDCN, with skin tissue biopsies demonstrating dense infiltration within the dermis and subcutis, composed of immature neoplastic blastoid cells, typically sparing the epidermis. Angioinvasion and coagulative necrosis can be minimal or absent (13). Furthermore, bone marrow aspirates showed extensive infiltration of elongated, tail-shaped end, basophilic cells with a blastoid nucleus and visible nucleolus, which are characteristic features of BPDCN (14).

As in our case, positivity for CD123, CD4, CD56, CD43, and CD45R on IHC and flow cytometry is insufficient for the final diagnosis. Specific antibodies such as CLA, TCL1, BDCA-2/CD303, CD2AP, BCL11a, and SPIB, and lack of expression of lineage-specific markers (CD3, CD14, CD16, CD19, CD20, MPO, and lysozyme), which our patient expressed, can help distinguish BPDCN from acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) (2,15).

Although our patient had a normal female karyotype (46, XX) upon cytogenetic analysis, previous studies have reported that approximately 60% of patients with BPDCN may have an abnormal karyotype, which has been identified as an independent predictor of poor survival outcomes in patients with BPDCN (16).

Until recently, first-line treatment for BPDCN mostly included intensive ALL-oriented chemotherapy regimens (hyper-CVAD); although the majority of patients had good initial responses, relapses were very frequent (17). In cases with CNS affection, a more favorable prognosis has been observed when prophylactic intrathecal chemotherapy was given (18). In 2018, FDA approved a novel CD123-targeted therapy (tagraxofusp-erzs), containing recombinant human interleukin-3 fused to diphtheria toxin, showing encouraging results with a high overall response rate and relatively durable remissions (20). Over the last few years, several new therapeutic approaches such as the use of chimeric antigen receptor (CAR) T-cells and BCL-2 inhibitors as a monotherapy or in combination with chemotherapy have shown promising results (21). Although further research is needed to fully understand the long-term effects of emerging therapies, their use may represent a significant advance in the treatment of BPDCN (20).

In conclusion, our case highlights the importance of considering less commonly affected gender and age groups in the diagnosis and treatment of rare and aggressive cancers like BPDCN. In this case, the

patient was a 45-year-old woman who presented with distinct clinical features that were initially misdiagnosed for 3 months, delaying the start of treatment. Furthermore, the patient had CNS involvement, which can act as a sanctuary site for cancerous cells and lead to disease recurrence even after successful treatment in other parts of the body. As a result, additional therapy is necessary to ensure clearance of the disease from the meningeal compartment and improve the patient's chances of a favorable outcome.

This case emphasizes the importance of effective management of BPDCN that requires a multidisciplinary approach, with close collaboration between dermatologists, hematologists/oncologist, neurologists, and other specialists. Although currently available therapies for BPDCN may lead to uncertain and unfavorable prognosis, prompt recognition and treatment with emerging innovative therapies may be essential for improving the outcomes of BPDCN.

Additionally, our patient had the misfortune to be diagnosed and treated during the COVID-19 pandemic; unfortunately, she had not received a COVID-19 vaccine before contracting SARS-CoV2 infection, and consequently developed severe respiratory disease and died, despite all the available therapies.

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