Blastic plasmacytoid dendritic cell neoplasm: a rare lymphoma of extremely aggressive course

Magdalena Żychowska[1], Aleksandra Batycka-Baran[1], Zdzisław Woźniak[2], Joanna Maj[1]

[1]Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland
[2]Department of Pathomorphology, Wroclaw Medical University, Wroclaw, Poland

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN), formerly known as blastic NK cell lymphoma or CD4+/CD56+ hematodermic neoplasm, is a rare aggressive disorder of a not fully understood etiology [1]. It predominantly involves the skin and has a high risk of leukemic dissemination [2]. The disease has an aggressive course and poor long-term prognosis with a median survival of 12–16 months [3]. We report a patient, who displayed clinical and immunohistochemical features of BPDCN with no primary bone marrow involvement. The disease had an extremely rapid course, which led to the patient's death in 4 months after the first lesions had developed.

A 70-year-old Caucasian male was referred to our Department in December 2014 with a 2-month history of rapidly developing asymptomatic nodules and plaques on the head, neck and upper part of the trunk. On physical examination, we saw disseminated red-to-purple indurated nodules and bruise-like plaques located predominantly within the head, neck and upper part of the trunk (Figure 1). The biggest plaques, located on the right cheek, chin and back were round, well-circumscribed, red-to-purple, had up to 7 cm in diameter and presented discrete scaling on the surface. Numerous smaller red and brownish indurated lesions were located within the face, back and chest. There were no signs of peripheral

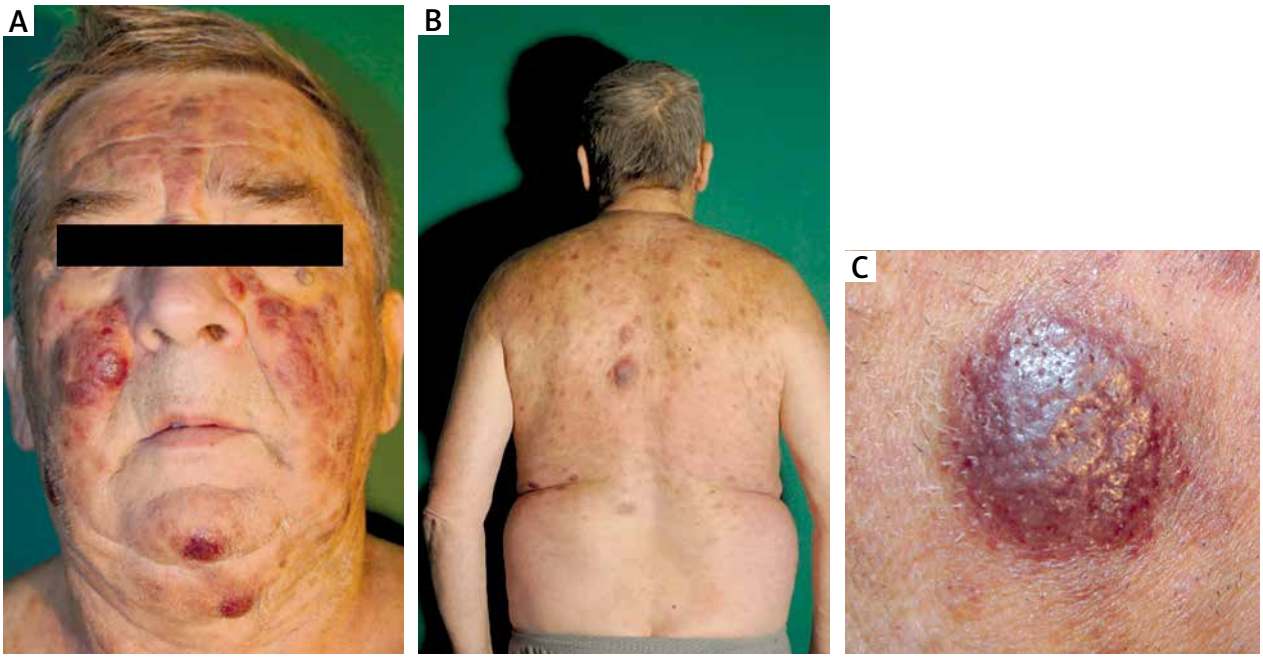

Figure 1. Clinical presentation of the patient. **A** – Red-to-purple nodules and plaques on the face. **B** – Disseminated red and brownish plaques on the upper part of the back. **C** – Red nodule on the right cheek (in magnification)

Address for correspondence: Magdalena Żychowska MD, Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, 1 Chałubińskiego St, 50-368 Wroclaw, Poland, phone: +48 669 422 237, e-mail: magda.zychowska@gmail.com
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lymphadenopathy. Basic laboratory work-up revealed leucopenia (WBCs 3.07 × 10^9/l) with thrombocytopenia (PLTs 102 × 10^9/l) and elevated levels of serum creatinine (1.5 mg/dl) and β2-microglobulin (6 mg/l). The chest X-ray was normal, while ultrasonography displayed hepatosplenomegaly and slight enlargement of the axillary lymph nodes. A 5-mm punch biopsy was performed. On histology, the specimen showed dense dermal and subcutaneous aggregates of small-to-medium sized pleomorphic T-cells with no features of epidermotropism. Immunohistochemically, the infiltration was CD3+/–, CD4–/+, CD5–/+, CD7–, CD8–/+, CD20–, CD30–, CD56+, CD123+ (Figure 2). The Ki-67 proliferation rate was 30–35%. The infiltration was negative for Ebstein-Barr virus. Bone marrow biopsy was within normal limits. Taking into consideration rapid progression of cutaneous lesions, the patient was qualified for systemic chemotherapy. However, during the second hospitalization, before chemotherapy was initiated, the number of white blood cells, red blood cells and platelets decreased significantly (WBCs 2.19 × 10^9/l, RBCs 2.72 × 10^{12}/l, PLTs 69 × 10^9/l). The patient's general state started to ameliorate rapidly with development of renal and cardiac insufficiency. The patient died of the multi-organ failure 4 months after the first lesions had developed.

The BPDCN is a relatively new condition described for the first time in 1994 and initially termed "agranular CD4+ natural killer cell leukemia" [4]. Several synonymous names were introduced in the past years, including blastic NK cell lymphoma [2] and CD4+/CD56+ hematodermic neoplasm [3]. In the 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues, BPDCN was positioned in the group of acute myeloid leukemia and related precursor neoplasms [4].

The BPDCN is an extremely rare condition comprising 0.44% of all hematological malignancies and 0.7% of cutaneous lymphomas [5]. Around 200 cases have been reported so far. The malignancy affects mainly older males with a median age at diagnosis of 67 years and a male to female ratio of 2.2 : 1 [6].

The skin is the most frequently involved organ in patients diagnosed with BPDCN, followed by the bone marrow and lymph nodes. Clinically, cutaneous lesions include non-pruritic purple tumors, nodules or bruise-like infiltrates. The skin may be the only organ involved at diagnosis, however, the involvement of bone marrow, lymph nodes and other sites including lungs and the central nervous system usually occurs with disease progression. More often, systemic dissemination is present at diagnosis [3]. Only a few cases of leukemic spreading without cutaneous involvement have been reported so far [7, 8]. Histologically, the infiltrate involves the dermis and subcutaneous tissue with no significant epidermotropism and is usually composed of medium-sized mononuclear cells resembling lymphoblasts or myeloblasts [9]. Neoplastic cells co-express CD4, CD43, CD45RA, CD56 and plasmatic dendritic cells-related antigens – CD123, T-cell leukemia 1 (TCL1), blood dendritic cell antigen 2 (BDCA 2), BDCA4, CD2AP and platelet endothelial cell adhesion molecule (CD31). Typically, B-cell markers (CD19, CD20, CD79a), T-cell markers (CD3, CD5) and stem cell markers (CD34, CD117) are negative. In rare cases, CD56 may be negative, which makes the diagnosis of BPDCN more challenging [1, 3, 4, 10].

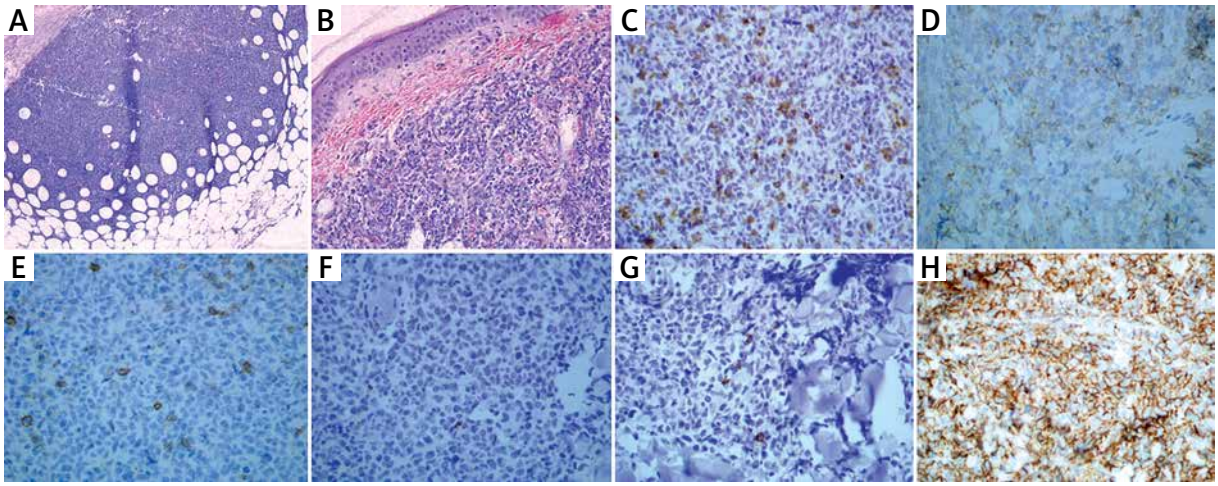

Figure 2. Histopathological and immunohistochemical findings. **A** – Dense lymphocytic aggregates infiltrating subcutaneous tissue (hematoxylin & eosin, magnification 40×). **B** – Neoplastic infiltrate consisting of small/medium-sized pleomorphic lymphocytes (hematoxylin & eosin, magnification 100×). The immunohistochemical staining disclosed: **C** – partial loss of CD3, **D** – diminished expression of CD4, **E** – partial expression of CD5, **F** – complete loss of CD7, **G** – negative anti-CD20 staining, **H** – high expression of CD56 (magnification 40×)

The etiology of BPDCN remains undetermined. According to data from literature, in 4 patients the onset of the malignancy was preceded by myelodysplastic syndrome and in 1 patient, an association with human T-cell lymphotropic virus 1 was suggested [8, 11]. No association with Epstein-Barr virus has been found so far [3].

The BPDCN was initially suggested to originate from immature NK cells [1, 2]. However, recent molecular studies have changed the approach to this malignancy and pointed to the potential connection with plasmacytoid dendritic cells [4]. Normal plasmacytoid dendritic cells stem from common myeloid or lymphoid progenitors and are characterized by a lineage (Lin) negative, HLA-DR+, CD56–, CD123+, CD11c– immunophenotype [3]. The BPDCN is currently believed to originate from precursor plasmacytoid dendritic cells and has a distinct CD56+ immunophenotype [3]. The diagnosis of BPDCN is based on morphological and cytological features with a characteristic immunophenotype of neoplastic cells expressing CD4, CD56, CD123, CD2AP markers and blood dendritic cell antigens 2 and 4 [3, 4].

Prognosis for patients diagnosed with BPDCN is poor with a median survival of 12–16 months [3]. The leukemic form of BPDCN and biallelic deletion of 9p21.3 (*CDKN2A/CDKN2B*) have been associated with a shorter survival rate, while patients with skin involvement at presentation, expression of CD303 and/or high Ki67 proliferative index are suggested to have better prognosis [10].

Non-Hodgkin lymphoma or acute lymphoblastic leukemia-type induction regimens are usually used as first-line chemotherapy. Both regimens have a response rate of approximately 90% but the durability of response is usually short and relapses refractory to further treatment are common [9]. Hematopoietic stem cell transplantation, particularly if it is performed at first remission, offers possible cure [3].

The BPDCN is a rare hematological malignancy, which primarily involves the skin. Dermatologists play an important role in rapid diagnosis of the neoplasm as they are usually the first physicians that patients refer to.

Conflict of interest

The authors declare no conflict of interest.

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