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CASE REPORT

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) — diagnostic and therapeutic challenge

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Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive haematological malignancy. The disease usually affects the skin, bone marrow, peripheral blood and less commonly lymph nodes. The actual incidence of BPDCN is currently unknown. The data presented in the literature most often relate to one cases or small groups of patients, rarely they are multicentre studies. Diagnosis of BPDCN is based on histopathological examination and immunohistochemical stains. The diversity of the clinical manifestations and the PBDCN immunophenotype is the cause of significant difficulties in making a diagnosis and can lead to diagnostic errors. The optimal treatment for patients with this cancer has not yet been established. Responses to various chemotherapy regimens are unsatisfactory. Recent literature has reported that bone marrow allograft or targeted therapy may improve treatment outcomes in this group of patients. The paper presents the case of a 75-year-old man with BPDCN diagnosis. Attention was paid to diagnostic difficulties in patients with BPDCN and the differentiation of this rare disease with other hematological malignancies was discussed. The need for a national register of BPDCN patients has been highlighted. This could contribute to expanding knowledge about this cancer and to the development of effective, standard therapeutic treatment.

Key words: plasmacytoid dendritic cells, chemotherapy, immunohistochemistry

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive malignancy originating from the precursors of plasmacytoid dendritic cells (PDC) [1]. The BPDCN nomenclature has evolved over years since the first description of this disease in 1994 by Adachi et al. [2]. In the revised World Health Organization (WHO) classification from 2017 BPDCN was characterized as a separate myeloid neoplasm [3].

Blastic plasmacytoid dendritic cell neoplasm mainly affects people in older age with a predominance of males and an incidence peak in the 6^{th}–7^{th} decade of life. There is no racial or ethnic predilection observed [4–7]. The pathogenesis of BPDCN is unknown. The disease usually affects the skin, bone marrow, peripheral blood and

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less commonly lymph nodes. To rarely described BPDCN localizations belong to the central nervous system, tonsils, liver, spleen, lungs, testicle, oral cavity [5, 8–10]. On FBC assessment, mild or moderate cytopenia is observed, while systemic symptoms are rare. BPDCN is characterized by an aggressive course and a poor prognosis. Median overall survival does not exceed 2 years [4, 9].

The diagnosis of BPDCN, depending on the original clinical presentation, is based on histopathology and immunohistochemistry (IHC) staining of biopsied sections of the involved sites, usually skin and/or bone marrow and flow cytometry (FCM) of bone marrow aspirate and/or peripheral blood [11].

The paper presents a case of a patient with BPDCN and a review of the literature on this rare disease.

Case report

A 75-year-old male was admitted to Mazowiecki Oncology Hospital in Wieliszew with suspected cutaneous lymphoma. On admission, numerous brown infiltrative-nodular lesions were found within the skin of the face, torso and lower limbs (Figure 1) and cervical, axillary and inguinal lymphadenopathy were present. The skin lesions had been persistent for several months according to the patient. The general condition of the patient was average (assessment according to the WHO scale) mainly due to pronounced general symptoms: fevers and increased sweating. Imaging test results of the chest and abdominal cavity were normal. On full blood count, moderate anaemia [haemoglobin (Hb) level 10 g/dL] and thrombocytopenia [platelet count (PLT) 72 × 10^9/L] were present. Leukocyte count was within normal values [white cell count (WBC) 7 × 10^9/L], blast cells were present (3%) on the blood film. Established in another centre histopathological diagnosis was descriptive and did not allow for an unambiguous diagnosis. The skin biopsy was consulted in the Department of Pathomorphology at MOH and then in the Synevo Department of Pathomorphology. Finally, BPDCN was diagnosed — skin infiltration by a precursor neoplasm of plasmacytoid dendritic cells with immunophenotype: CD3–,CD4+/–, CD56+, CD123+, CD14–, CD163– CD30–, CD34–, CD68–, CD8–, MPO–, PAX-5–,S100–, TDT–, Ki67 20–25% (Figure 2) Because of abnormal blood film, bone marrow biopsy was carried out for cytology assessment as well as immunophenotyping and cytogenetic testing on the bone marrow was performed. In an extremely hypercellular sample infiltration with monomorphic immature undifferentiated cells was found, accounting for 80% of marrow aspirate cells. Bone marrow flow cytometry revealed the presence of a dominant clonal cell population with the phenotype: CD4+, CD56+, HLA-DR+, CD117+, CD123+, CD3–, CD8–, CD16–, CD38–, CD138–,CD13–, CD33+/–, CD14–, CD15–, Cd11b–, MPO–,CD64–, CD34–. Thus, infiltration of the bone marrow by precursor neoplasm of blastic plasmacytoid dendritic cells was confirmed. Bone marrow cytogenetics showed abnormal male hyperdiploid karyotype 50,XY,+7,+18,+21,+22(12)/46,XY. The patient was qualified for a treatment protocol similar to that used to treat acute myeloid leukaemia (AML). Due to the patient's advanced age and co-morbidities (history of myocardial infarction, paroxysmal atrial fibrillation, chronic obstructive pulmonary disease), anthracyclines were excluded from the treatment regimen. The first treatment protocol given contained cytosine arabinoside 100 mg/day intravenously (i.v.) for 7 days. The treatment was successful and the patient was discharged home in good general condition. After initial partial (> 50%) regression of skin lesions, present lesions got larger and new nodular-infiltrative cutaneous changes appeared within the skin of the limbs and trunk in the following weeks. The patient received a second course of treatment containing again cytosine arabinoside in a total dose of 100 mg/day i.v. for 7 days and additionally etoposide in a total dose of 100 mg/day i.v. for 3 days. That therapy was complicated by pancytopenia and septic shock. The patient was hospitalized in a haematology department of a district hospital where he passed away despite intensive therapy.

Discussion

The actual prevalence of BPDCN is currently unknown. Most previous reports present single cases or small cohorts of patients [5, 6, 8, 12–14]. In recent years articles reporting on numerous groups of patients with this neoplasm were published [4, 10, 15]. So far, the most numerous cohort of 379 patients with BPDCN was described by American authors who based on the analysed data report the annual incidence of this neoplasm in the US population being 0.45/1,000,000 [15]. In Poland, 17 patients with BPDCN were reported [12, 13]. Presented in the literature data most often relate to the material analysis of one centre [5, 6, 8, 12–14], less often those are multicentre studies [8, 14, 16]

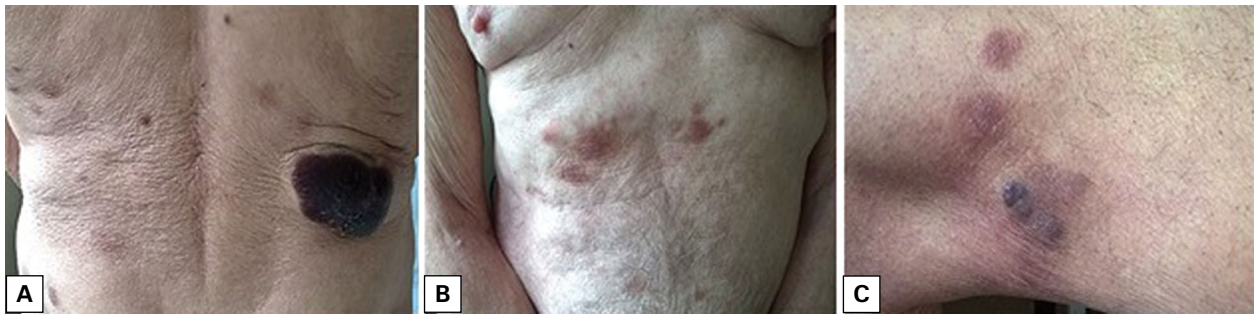

Figure 1A–C. Numerous nodules and infiltrative lesions on the skin of the limbs and trunk

or derived data from cancer patient databases [Surveillance Epidemiology, and End Results Program (SEER), National Cancer Database (NCDB)] [15]. The database of patients with BPDCN treated in Polish haematology centres comes from the Polish Leukaemia Treatment Group.

In the case presented in this paper, the main symptom of the disease were skin lesions. According to most reports, skin lesions occur in nearly 90% of patients with BPDCN [6, 8, 10, 12]. A lower percentage of cases with skin involvement of 64% was observed by Martin-Martin et al. [17]. According to the authors, the reason for this discrepancy is the underdiagnosis of cases with non-cutaneous disease localization [17]. In the available literature, only a few BPDCN cases without skin involvement have been described, usually with a primary leukaemic presentation [5, 18, 19].

The presented case and experiences of other authors prove that in patients with BPDCN after the initial period of remission the disease relapses early leading to rapid worsening of the patient's condition. According to data presented in the literature, disease relapse is manifested, among others, by neoplastic skin and bone marrow infiltrates and often central nervous system (CNS) involvement [6, 8]. CNS involvement has been observed in approximately 10% of BPDCN patients at the time of diagnosis [8–10, 17] and in nearly 30% in relapsed cases [8, 9, 17]. Martin-Martin et al. suggest a much higher percentage of BPDCN cases with CNS involvement at the time of diagnosis. According to the authors of the cited report, the management protocol of patients with BPDCN should include assessment of the cerebrospinal fluid at diagnosis and prophylactic intrathecal chemotherapy [20].

Tumour cell immunophenotyping plays an important role in disease diagnosis. Literature data emphasize an immunophenotypic heterogeneity of this neoplasm. BPDCN cells are characterized by CD4 and CD56 expression and specific markers of dendritic cells (CD123, CD43, BDCA-2/CD303 and TCL1) [1]. The result of immunohistochemical staining in the presented patient (CD4+, CD56+, CD123+) confirms these observations. However, in a small percentage of cases, CD56 were not expressed [6, 16], which raises a question of the usefulness of this marker in BPDCN diagnostics. The authors agree that the lack of CD56 expression should not rule out the diagnosis of this malignancy [1]. Moreover, present in most cases positive result for CD4 and CD123 is not specific for BPDCN diagnosis [6]. Research is currently conducted to search for new highly specific immunohistochemistry markers for BPDCN [21, 22].

Immunophenotypic diversity of BPDCN makes it considerably difficult to get the right diagnosis and can lead to diagnostic mistakes. The immunohistochemical profile of BPDCN may mimic that observed in the cutaneous localization of AML. Expression of CD4 and other antigens of T lineage on BPDCN cells requires differential with lymphoblastic T-cell leukaemia/lymphoma (T-ALL/LBL, T-cell acute lymphoblastic leukaemia/lymphoma). It also remains a diagnostic challenge to differentiate BPDCN with extranodal NK/T cell lymphoma, nasal type (ENKTCL) [1].

The optimal method of treatment of patients with BPDCN has not yet been established. The neoplasm is rarely diagnosed and response to various forms of treatment is short-term. Initially, chemotherapeutic regimens given to treat acute lymphoblastic leukaemia and non-Hodgkin's lymphomas were eagerly used. However, in recent years, therapies to treat AML are used more often [23]. Due to the aggressive clinical course and myeloid origin of the neoplasm, the presented patient was qualified for treatment with a chemotherapy regimen used for the treatment of AML, adapted

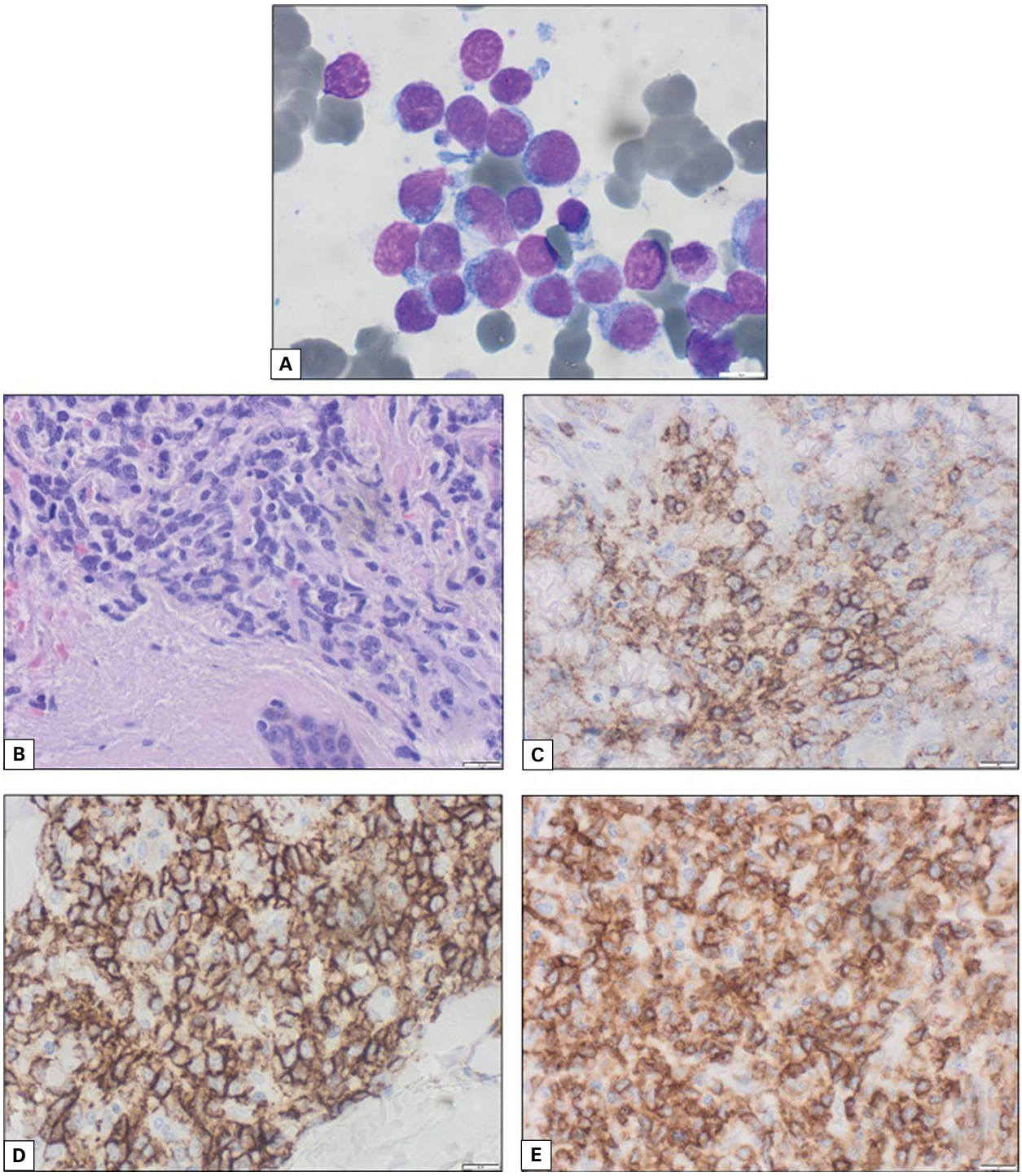

Figure 2A. Bone marrow aspirate. There are numerous blast cells with a narrow layer of the cytoplasm, immature chromatin and irregular nuclear outline (Wright–Giemsa stain, magnification ×1000). **B–E.** Histopathological images and immunohistochemical staining of a skin lesion. Hematoxylin and eosin staining (magnification ×400) shows infiltrate of monomorphic medium-sized immature cells. Immunohistochemical expression of the CD4 (**C**), CD56 (**D**), CD123 (**E**) markers is positive on tumor cells

to the patient's age and his co-morbidities. According to some authors, the optimal form of management seems to be an implementation of intensive induction chemotherapy followed by allogeneic transplantation of haematopoietic cells in case of disease remission [13, 24].

Older patients in the poor general condition who are not eligible for transplant should receive symptomatic treatment or mild forms of chemotherapy. In this group of patients chemotherapy according to COP (cyclophosphamide, vincristine, prednisone) regimen was administered with possibly adjuvant radiotherapy to involved skin lesions. Monotherapy with hydroxyurea, mercaptopurine, etoposide or prednisone can also be considered. According to available literature data such treatment allowed to obtain satisfactory responses in most patient cases, but median overall survival was short and lasted 9 months. A satisfactory (positive) response was defined as: bone marrow blasts percentage less than 5%, normal neutrophil and platelet count in peripheral blood, presence of residual skin lesions, resolution of lymphadenopathy and splenomegaly [23]. In recent years, reports on the effectiveness of azacitidine in the treatment of BPDCN were published [25, 26].

It appears that options of conventional chemotherapy in the treatment of BPDCN are limited, therefore, effective targeted therapies are sought. In December 2018, the American Food and Drug Administration Agency (FDA) approved for the treatment of patients with BPDCN a drug called Elzonris® (tagraxofusp-erzs), which is a recombinant interleukin 3 linked to diphtheria toxin protein. It binds to the IL-3 receptor α (CD123) overexpressed by BPDCN cells. The results of a prospective research study prove that targeted anti-CD123 therapy can significantly improve the results of treatment in this group of patients [27]. Optimal therapeutic management of patients with BPDCN remains a challenge.

Summary

Blastic plasmacytoid dendritic cell neoplasm is a rare haematological malignancy with poor prognosis, diagnosis of which is difficult due to clinical and phenotypic heterogeneity.

Present in most cases of BPDCN expression of CD123+, CD56+, CD4+ antigens is not specific for this neoplasm, which calls for the need to search for new diagnostic markers.

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