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**Case report / Приказ болесника**

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**Blastic plasmacytoid dendritic cell neoplasm of the uterus**

Бластична плазмоцитодина дендритична неоплазма материце

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## Blastic plasmacytoid dendritic cell neoplasm of the uterus

### Бластична плазмоцитодина дендритична неоплазма материце

#### SUMMARY

**Introduction** Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is rare and very aggressive hematological malignancy derived from precursor of the plasmacytoid dendritic cell (pDC). We present a case with cervix uteri involvement without skin lesions, and to our knowledge, it is the first case of BPDCN localized in the cervix.

**Case Outline** A 66 year-old, previous healthy woman, initially presented with a 4-weeks history of vaginal bleeding. Gynaecological examination showed tumorous bleeding formation on cervix uteri. Except paleness of skin, the physical examination was normal. Complete blood counts showed anaemia and thrombocytopenia. Computed tomography (CT) scans disclosed expansive tumorous formation in the level of the isthmus and cervix uteri 60x42mm in diameter. Cervical biopsy was done and final pathohistological diagnosis was BPDCN. Karyotype analysis results from the bone marrow aspiration specimen demonstrated tetrasomy of chromosome 2 and monosomy of chromosome 16. The patient did not accept treatment and died two months after initial diagnosis was established.

**Conclusion** Attributes as aggressive clinical course of BPDCN, demonstrated unusual localisation, infrequency and the absence of consensus about standard treatment options, demand constructive clinical reasoning and tight cooperation between medical professionals of various fields.

**Keywords:** BPDCN, hematologic malignancy, aggressive

#### САЖЕТАК

**Увод** Бластична плазмоцитодина дендритична неоплазма (БПДЦН) представља редак и врло агресиван хематолошки малигнитет који потиче од прекурсора плазмоцитодне дендритичне ћелије (пДЦ). Презентујемо случај захватања грлића материце БПДЦН, без кожных лезија. Према нашим сазнањима, ово је први забележен случај БПДЦН локализован у грлићу материце.

**Приказ болесника** Претходно здрава жена, стара 66 година, иницијално се презентовала са крварењем из усмине. Гинеколошким прегледом је уочена крварећа туморска формација грлића материце. Осим блеће пребојности коже, физикални налаз је био уредан. У крвној слици су уочене анемија и тромбоцитопенија. Компјутеризованом томографијом је радиолошки верификована експанзивна туморска формација грлића материце промера 60x42мм. Потом је урађена биопсија наведене промене, а ПХ налаз је показао да се ради о БПДЦН. Анализом кариотипа из аспирира ћелија коштане сржи је утврђена тетразомија хромозома 2 и монозомија хромозома 16. Пацијенткиња је одбила третман и преминула након два месеца од постављања дијагнозе БПДЦН.

**Закључак** Агресиван клинички ток БПДЦН, поменута неубичајена локализација, ретка болест и недостатак консензуса о стандардним терапијским опцијама, захтевају конструктивно клиничко резонување и сарадњу медицинских професионалаца из различитих области.

**Кључне речи:** БПДЦН, хематолошки малигнитет, агресивна

## INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is rare and very aggressive hematological malignancy derived from precursor of the plasmacytoid dendritic cell (pDC) [1]. First it was described in mid-1990s and formerly was known as haematodermic neoplasm and blastic natural killer lymphoma [2–4]. In 2008, WHO classification for hematopoietic tumors it was categorized under “acute myeloid leukemia and related precursor neoplasm” [5]. However, in the 2016. WHO myeloid neoplasm and acute leukemia classification, BPDCN is distinguished as separate entity, in contrast to the previous classification [6]. BPDCN is characterized by high frequency of cutaneous involvement at diagnosis which can be only clinical manifestation at the beginning [7]. Bone marrow and lymph nodes

involvement is observed in about 50% of cases [8]. Minority of cases initially present with acute leukemia, but more often leukemia is presentation of advanced disease [9]. Other rarely places of BPDCN localization are spleen, liver, central nervous system, tonsils, lungs, kidneys and muscles [7]. We present a case with cervix uteri involvement without skin lesions, and to our knowledge, it is the first case of BPDCN localized in cervix.

## CASE REPORT

A 66 years-old, previous healthy women, initially presented with a 4-weeks history of vaginal bleeding. Gynecologic examination showed tumorous bleeding formation on cervix uteri. Except paleness of skin, the physical examination was normal. Complete blood counts showed bicytopenia (hemoglobin 10 g/dL, platelet count 29000/mm<sup>3</sup>, and white blood cell count 6500/mm<sup>3</sup>). Routine hemostasis screening tests were normal (international normalized ratio 1.17, fibrinogen 2,03g/l, activated partial thromboplastic time 34sec, D-dimer 299µg/l). Lactate dehydrogenase was elevated at 1777 U/L while other components of biochemical panel were in reference range. Computed tomography (CT) scans disclosed expansive tumorous formation in the level of the isthmus and cervix uteri 60x42mm in diameter which invades all the layers of uterus and partly propagated by periuterine adipose tissue (Figure 1). CT also revealed multiple enlargements of iliac, retroperitoneal, mediastinal lymph nodes with peritoneal nodular formations.

Cervical biopsy was made and pathohistological examination of specimen showed diffuse infiltration of mucosa with uniform small to medium size cells with blast-like morphology. Tumor cells predominantly occupy the cervical stroma sparing the squamous epithelium. The cells showed large, irregular, oval nuclei with finely granulating chromatin, one or more nucleoli and scant and agranular cytoplasm (Figure 2: A, B, C). Immunohistochemical staining were performed on formalin-fixed, paraffin-embedded tissue.

Tumor cells co-expressed, CD4, CD43, CD56, CD123, CD45, CD33 and showed partial positivity for CD68 (Figure 2: D, E, F, G, H). One part of nuclei also was positive on p16 and Oct-2. Cells were negative on Vimentin, TdT, CD34, CD117, CK5, CK7, p63, p16, SM Actin, Synaptophysin, PGP 9.5, Chromogranin A, PAX-5, CD79a, CD20, CD10, MUM-1, CD138, CD30, CD15, CD2, CD3, CD5, CD7, CD8, Granzyme B, Perforin, CD13, MPO, CD14, CD163, bcl-2, bcl-6. Final pathohistological diagnosis was BPDCN.

Bone marrow biopsy showed a slightly hypercellular marrow, with CD4, CD56, CD123 positive large blast cells accounting for 5-7% of cellularity. Lymphoid, NK and myeloid lineage associated antigens were negative.

Karyotype analysis results from the bone marrow aspiration specimen demonstrated tetrasomy of chromosome 2 and monosomy of chromosome 16 in 12 out of 20 analyzed metaphase cells. (47,XX,+2,+2,-16[12]/46,XX[8]).

Based on clinical, radiographic and predominantly on histological and immunohistochemical findings of cervical and bone marrow biopsy, patient was diagnosed with BPDCN, but patient refused further treatments and die two months after initial diagnosis was established.

## DISCUSSION

BPDCN is a very rare and aggressive form of lymphoma-like disease derived from precursor of the pDC. Diagnosis is made based on clinical presentation and histological and immunophenotype features of involvement tissue. In majority of cases it presents with indolent cutaneous lesions followed later with dissemination and bone marrow and lymph node involvement [10]. Minority of cases present with fulminant leukemia without skin infiltration. Biopsy of involvement tissue usually revealed medium-sized blast cells with irregular nuclei, fine chromatin, and at least one small nucleolus. The cytoplasm is scant and

agranular. Because of the overlap with other hematopoietic neoplasms such as myeloid sarcoma/acute myeloid leukemia, T-cell lymphoblastic leukemia/lymphoma, NK-cell lymphoma/leukemia extensive immunophenotype analysis is necessary [7,10,11]. Recent multicentric study suggested that triple positive CD4+CD56+CD123+ phenotype associated with negativity for lineage-specific markers such as markers for B cells (CD20, CD79a), T cells (CD3), myeloid cells (myeloperoxidase) and monocytes (CD11c, CD163, lysozyme) is a minimum requirement for defining BPDCN [12].

Our patient presented with quite unique localization of BPDCN in cervix and isthmus uteri. Originate of tumor cells stay questionable, if it is in bone marrow or in cervical mucosa, because BPDCN has an aggressive clinical presentation that probably affects both sites either consecutively or simultaneously. Histopathological features and triple positive (CD4+CD56+CD123+) phenotype in absence of specific lineage markers clearly ensign on BPDCN. However, the diagnosis criteria varied from study to study but majority of them included these 5 markers: CD4, CD56, CD123, CD303 (also known as BDCA-2) and TCL1 [10]. Heterogeneity of BPDCN tumor cells is more emphasized by occasional CD56 and/or CD123 surface marker expression [7,11]. Interesting fact is that blasts with immature plasmacytoid dendritic cell phenotype presents typically without extramedullary (e.g. skin) disease at presentation, on the other hand, mature blast cell phenotype more frequently display skin/extramedullary involvement [13]. However, a few myeloid-associated antigens have been seen in a significant number of cases [11]. It is highly important to diagnostically differentiate BPDCN from acute myeloid leukemia (AML) or AML associated leukemia cutis or myeloid sarcoma. BPDCN is characterized by pDC antigens positivity, CD123 and TCL-1, and myeloperoxidase (MPO) negativity, while AML or myeloid sarcoma show MPO positivity and negativity for pDC antigens [14]. In particular, CD68, an antigen typically expressed by granulocytes and histiocytes as well as normal plasmacytoid dendritic cells, is

noted in significant number of cases [11]. Another myeloid antigen frequently found in the BPDCN neoplastic cells is CD33, which is most frequently reported myeloid marker expressed by BPDCN neoplastic cells [11]. Other strong myeloid markers expression, CD13 and CD117, has also been reported [10]. Neoplastic cells in our case show positivity on both antigen, as well as on CD45 and CD43 which are also often positive on BPDCN cells [10,11]. Similar triple positive (CD4+CD56+CD123+) cells with blast morphology were found in bone marrow, indicated bone marrow involvement.

Cytogenetic analysis frequently reveals complex aberrations seen in acute myeloid leukemia or myelodysplastic syndromes [11]. Interesting fact is that at the time of diagnosis two thirds of patients shows cytogenetic anomalies [10]. Recent studies showed several structural and numeral aberrations of chromosome as well as gene mutation associated with BPDCN. Most frequent recurrent genomic loses that are being published in are next: 5q21 or 5q34, 12p13, 13q13-21, 6q23, monosomy 15 and monosomy 9 [10, 11]. As mentioned above, BPDCN cells can carry multiple genetic abnormalities that overlap with the genetic abnormalities of myeloid and lymphoid neoplasms, but tetrasomy of chromosome 2 and monosomy of chromosome 16 described in this case are not one of them and influence of this numeral chromosomal aberration on etiology and pathogenesis of BPDCN is unknown.

Because of low incidence, there are no consensus for optimal therapy for BPDCN. The aim of treatment should be achievement of complete remission (CR) after first-line treatment based on protocols for acute myeloid leukemia or acute lymphoblastic leukemia and, after that, consolidation with allogeneic hematopoietic stem cell transplantation (allo-HSCT). Recent study confirms that the combination of methotrexate (MTX) and asparaginase for frontline treatment could be good solution with a low toxicity profile, even in elderly patients [10,12]. Having in mind that the CD123 positivity occurs in virtually all cases, using of specific BPDCN CD123-directed cytotoxin (Tagraxofusp) consisting of recombinant

human interleukin-3 fused to a truncated diphtheria toxin could be reasonable option for treatment. Based on results of study published by Pemmaraju et al. Tagraxofusp was approved as the only treatment specifically indicated for untreated or relapsed BPDCN patients with potential development of adverse events as well as included capillary leak syndrome, hepatic dysfunction and thrombocytopenia [15, 16].

**Ethical standards:** Written consent for publication of this article has been obtained by the patient's family member.

**Conflict of interest:** None declared.

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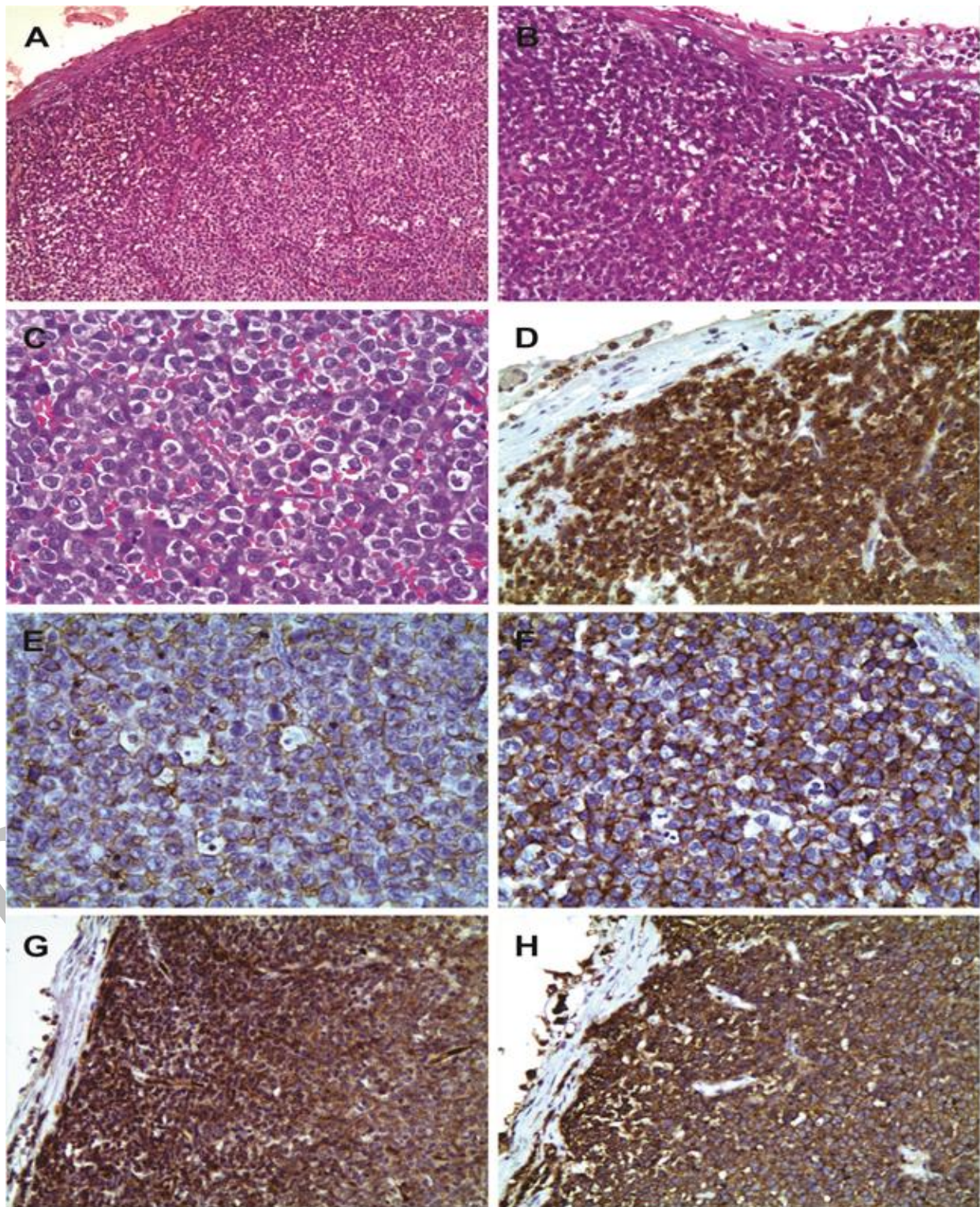




**Figure 1.** Computed tomography scans showed 60 mm mass in the level of the isthmus and cervix uteri, which invades all the layers of uterus and partly propagated by periuterine adipose tissue

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**Figure 2.** The patient's cervix pathohistology and immunohistochemistry; Hematoxylin and Eosin staining showed small to medium-sized blastoid cells diffusely infiltrating predominantly cervical stroma, sparing the epithelium (A, B, C). Immunohistochemically, tumor cells were positive for CD4 (D), CD43 (E), CD 56 (F), CD 123 (G), CD45 (H).