Paper Accepted

Case report / Приказ болесника

Predrag Djurdjevic¹, Zeljko Todorovic¹, Danijela Jovanovic¹, Ivan Cekerevac¹, Ljiljana Novkovic¹, Slobodanka Mitrovic², Vesna Cemerikic³, Vladimir Otasevic⁴, Darko Antic⁴,⁵,†

Blastic plasmacytoid dendritic cell neoplasm of the uterus
Бластична плазмоцитодина дендритична неоплазма материце

¹University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Internal medicine;  
²University of Kragujevac, Serbia, Faculty of Medical Sciences, Department of Pathology;  
³Beo-lab, Belgrade, Serbia;  
⁴Clinical Center of Serbia, Clinic for Hematology, Belgrade, Serbia;  
⁵University of Belgrade, Faculty of Medicine, Belgrade, Serbia

Received: November 11, 2019
Revised: April 10, 2020
Accepted: May 7, 2020
Online First: May 13, 2020
DOI: https://doi.org/10.2298/SARH191111027D

*Accepted papers are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the Serbian Archives of Medicine. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author’s last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

†Correspondence to:
Darko ANTIC
Clinical Center of Serbia, Clinic for hematology, Belgrade, Serbia
Email: darko.antic1510976@gmail.com
**Blastic plasmacytoid dendritic cell neoplasm of the uterus**

**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 tetrasyom 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 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

**САЖЕТАК**

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

**Приказ болесника** Претходно здрава жена, стара 66 години, иницијално се презентовала са крварењем из усмине. Гинеколошким прегледом је уочена крварећа туморска формација на грлићу материце. Осим блеђе пребојености коже, физикални налаз је био уредан. У крвној слици су уочене анемија и тромбоцитопенија. Компјутеризованом томографијом је радиолошки верификоване експанзивне туморске формације грлића материце промера 60x42мм. Потом је урађена биопсија и ПХ налаз је показао да се ради о БПДЦН. Анализом кариотипа из аспирата ћелија коштар الدكت питания се 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 неуобичајена локализација, ретка болест и недостатак консензуса о стандардним терапијским опцијама, захтева конструктивно клиничко резоновање и сарадњу медицинских професионалаца из различитих области.

**Кључне речи:** БПДЦН, хематолошки малигнитет, агресивна
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/mm3, and white blood cell count 6500/mm3). Routine hemostasis screening tests were normal (international normalized ratio 1.17, fibrinogen 2.03 g/l, activated partial thromboplastic time 34 sec, D-dimer 299 μg/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 60x42 mm 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. The 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, Synaptophisin, 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 a 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.
REFERENCES

1. Herling M, Jones D. CD4+/CD56+ hematodermic tumor: the features of an evolving entity and its relationship to dendritic cells. Am J Clin Pathol. 2007;127(5):687–700. DOI: 10.1309/FY6PK436NBK0RYD4. PMID: 17439829

2. Adachi M, Maeda K, Takekawa M, Hinoda Y, Imai K, Sugiyama S, et al. High expression of CD56 (N-CAM) in a patient with cutaneous CD4-positive lymphoma. Am J Hematol. 1994;47(4):278–82. PMID: 7526680

3. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768–85. DOI: 10.1182/blood-2004-09-3502. PMID: 15692063

4. Chan J, Jaffe E, Ralfkiaer E. Blastic NK-cell lymphoma. In Jaffe ES, Harris NL, Stein H VJ, editor. World Health Organization Classification of Tumors Pathology & Genetics Tumours of Haematopoietic and Lymphoid Tissues. London: IARC Press; 2001. p. 22–5.

5. Facchetti F, Jones D PT. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow S, Campo E HN et al., editor. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2008. p. 145–7.

6. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405. DOI: 10.1182/blood-2016-03-643544. PMID: 27069254

7. Riaz W, Zhang L, Horna P, Sokol L. Blastic plasmacytoid dendritic cell neoplasm: update on molecular biology, diagnosis, and therapy. Cancer Control. 2014;21(4):279–89. DOI: 10.1177/107327481402100404. PMID: 25310209.

8. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405. DOI: 10.1182/blood-2016-03-643544. PMID: 27069254

9. Laribi K, Denizon N, Besançon A, Farhi J, Lemaire P, Sandrini J, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm: From Origin of the Cell to Targeted Therapies. Biol Blood Marrow Transplant. 2016;22(8):1357–67. DOI: 10.1016/j.bbmt.2016.03.022. PubMed PMID: 27026248.

10. Zhang Y-W, Zhong J-H, Chen X-L, Xiao F, Chen F-Y. Blastic plasmacytoid dendritic cell neoplasm: A case report and literat
gen. Exp Ther Med. 2016;12(1):319-322. DOI: 10.3892/etm.2016.3259. PMID: 27347056

11. Garnache-Ottou F, Vidal C, Bichlé S, Renosi F, Poret E, Pagadoy M et al. How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients? Blood Adv. 2019;3(24):4238–4251. doi: 10.1182/bloodadvances.2019000647. PMID: 31869411;

12. Shi Y, Wang E. Blastic plasmacytoid dendritic cell neoplasm: a clinicopathologic review. Arch Pathol Lab Med. 2014;138(4):564–9. DOI: 10.5858/arpa.2013-0101-RS. PMID: 24678689.

13. Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. Br J Haematol. 2016;174(2):188–202. DOI: 10.1111/bjh.14146. PMID: 27264021

14. Wang Wei, Li W, Jia J-J, Zheng Yan, Wang Hao, Gao X-M, et al. Blastic plasmacytoid dendritic cell neoplasm: A case report. Oncol Lett. 2015;9(3):1388–92. PMID: 22236870. DOI: 10.1159/000334703

15. Sullivan JM, Rizzieri DA. Treatment of blastic plasmacytoid dendritic cell neoplasm. Hematol Am Soc Hematol Educ Progr. 2016;2016(1):16–23. DOI: 10.1182/asheducation-2016.1.16. PMID: 27913457

16. Pemmaraju N, Lane AA, Sweet KL, Stein AS, Vasu S, Blum W et al. Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm. N Engl J Med. 2019;380(17):1628-1637. doi: 10.1056/NEJMoa1815105. PMID: 31018069.

17. Haddadin M, Taylor J. Chemotherapy Options for Blastic Plasmacytoid Dendritic Cell Neoplasm. Hematol Oncol Clin North Am. 2020;34(3):559–92. PMID: 32336418. DOI: 10.1016/j.hoc.2020.01.011.
**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.
**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).