Blastic Plasmacytoid Dendritic Cell Neoplasm: Case Report and Literature Overview

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Abstract
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a malignancy with high frequency of skin involvement. A 39-year-old Caucasian female was suffering from weakness, myalgia, and skin eruption, which appeared during treatment of chlamydiosis with antibiotics in July 2016. Based on clinical presentation, laboratory investigations, and histological examination of skin and bone marrow biopsy, a diagnosis of BPDCN with the involvement of skin, bone marrow, and central nervous system was made. The patient was put on acute lymphoblastic leukemia-like chemotherapy and achieved complete remission in November 2016, the eruption regressed. In January 2017, allogeneic bone marrow transplantation from matched sibling was performed. Since May 2017, the cutaneous relapse with loss of CD56 expression has developed. This clinical case demonstrates the importance of laboratory tests. Histological examination helps to clarify a diagnosis of cutaneous lymphoma; however, a specific type of lymphoma needs immunohistochemical analysis. In our case, BPDCN at the initial stage presented like a systemic vasculitis.

Key Words: Blastic plasmacytoid dendritic cell neoplasm, cutaneous lymphoma, cutaneous oncology

Introduction
Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a malignancy with high frequency of skin involvement.[1] It develops from the plasmacytoid dendritic precursors of the myeloid line. Dendrocytes (DCs) are divided into two subtypes: classical CD11c+/CD123− cells and CD123+/CD11c−. Cells from the first subtype are presnter cells whose main function is triggering the primary immune response through the activation of naive T-lymphocytes via IL-12. DCs of the second type play an important role in antiviral defense through production of interferon-1. Plasmacytoid dendritic cells are absent in normal skin but migrate to the skin during wound healing, infections, inflammation, and neoplasms.[2]

The first published case of BPDCN was described by Adachi et al. in 1994. Previously known as NK-cell blastic lymphoma, it is three times more prevalent in men than in women and occurs primarily in patients older than 60 years, even though the disease can manifest at any age.[3] Prognosis is poor; the average survival rate is 14 months, with a 2-year survivability of 33% among patients, and a 5-year survival rate of 6%.[1]

Case Report
A 39-year-old Caucasian female was suffering from weakness, malaise, numbness of the distal parts of the limbs, weakness in the hands, myalgia, and skin eruption. At the time of examination (September, 2016), the eruption was presented with multiple sharply marginated bluish dense papules, prominent over the skin surface. The patient had edema of the shins. During regular medical examination in May 2016, leukopenia of 1.9 × 10⁹/l and hemoglobin 98 g/l were observed. The rash first appeared during treatment of chlamydiosis with antibiotics in July 2016. The eruption presented with scarlet papules on the skin of shins and forearms. Systemic vasculitis was diagnosed; lymphoma was not included in differential diagnosis. The patient was treated with methylprednisolone 25 mg and prednisolone 25 mg per day with no effect. In September, condition of the patient worsened, and the eruption became widespread...
In the analysis of blood, pancytopenia increased, so then a bone marrow examination and a biopsy of skin were performed. The bone marrow aspirate showed infiltration of atypical lymphoid cells of medium and large sizes with a rounded nucleus, variable basophilic cytoplasm, reduced hematopoietic cells including loss of megakaryocytes. The immunohistochemical examination showed positive expression of CD4, CD56. Skin biopsy showed a massive monomorphic infiltration of medium-sized cells with moderately polymorphic dispersed chromatin, a narrow cytoplasm all over the dermis and subcutis. Nuclei were clear, and a significant amount of mitosis was observed. There were no signs of epidermotropism [Figure 3]. Cells were characterized by positive immunohistochemical reactions for CD4, CD56, S100, Ki67 (70%) [Figure 4]. Cytology analysis of cerebrospinal fluid showed similar tumor cells. Based on these findings, a diagnosis of BPDCN with involvement of skin, bone marrow, and central nervous system was made. The patient was started on acute lymphoblastic leukemia-like chemotherapy (I induction phase: dexamethasone, daunorubicin, vinblastine, L-asparaginase; II induction phase: purinethol, endoxan, cytosar, L-asparaginase), with intrathecal administration of methotrexate, cytarabine, and dexamethasone.

The patient achieved complete remission in bone marrow and central nervous system when tested in November 2016, and the eruption regressed completely. In January 2017, allogeneic bone marrow transplantation from matched sibling was performed. Since May 2017, the relapse of only the skin lesions had developed. Immunohistochemical examination showed a loss of CD56 expression, which was unusual.

**Discussion**

BPDCN is an extremely rare disease; therefore, the clinical features are described primarily in only a few published clinical cases. A literature review made it possible to reveal certain characteristics of this pathology.

The disease manifests as an eruption in 90% of all cases. Typically, the eruption is widespread, presents in the form of papules, plaques, nodules with clear demarcation of brownish-red, purple, or cyanotic color. The rash is often itchy, painful, but may be asymptomatic. The size of these elements varies from a few millimeters to 3–4 cm. In rare cases, nodules and

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**Figure 1:** Cutaneous changes on the shins

**Figure 2:** Cyanotic-pink dense papules and plaques at the initial presentation

**Figure 3:** Skin biopsy found a massive monomorphic infiltration of medium-sized cells with no signs of epidermotropism (H and E, ×40 and ×100)

**Figure 4:** Immunohistochemical staining of skin biopsy showing diffusely positive CD4, CD56, S100, Ki-67 cells with proliferative activity 70% (×400)
plaques with a diameter of up to 10 cm have been observed. The disease may also present as erythema, hyperpigmentation, purpura, or ulcers with necrosis. Mucous membranes are rarely involved and only observed in 10% of patients. The described clinical case clearly demonstrates the characteristics of BPDCN. The disease manifested with leukopenia and anemia. A skin lesion appeared after 2 months characterized by scarlet papules on the legs and forearms. Within 4 months, rash had become widespread. The eruption finally presented with multiple sharply marginated bluish dense papules, prominent over the skin surface [Table 1].

Table 1: Published cases of blastic plasmacytoid dendritic cell neoplasm

| Authors            | Patient's age, gender | Skin eruption                                                                 | Involving other organs                                      | First appearance                                                                 |
|--------------------|-----------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------|
| Dantas et al. 2011 | Female, 68            | -                                                                             | Liver, spleen, bone marrow                                   | Dizziness, dyspnea, mental confusion, hepatomegaly, splenomegaly, anemia       |
| Zhang et al. 2016  | Female, 26            | -                                                                             | Bone narrow                                                  | Pancytopenia, headache, earache and cough                                        |
| Chou et al. 2014   | Male, 41              | Multiple 2-3 cm in diameter bluish to violaceous infiltrated patches, plaques on trunk, few irregularly shaped violaceous plaques on cheeks | Nasopharyngeal tissue                                        | Multiple asymptomatic bruise-like lesions on his trunk and face, bleeding in the right nasal cavity |
| Döger et al. 2011  | Male, 62              | 2 well-demarcated erythematos plaques on the trunk, 6 purple-red papules on the back and upper extremities | Right axillary lymph node                                   | Well-demarcated erythematos plaques on the trunk, purple-red papules on the back and upper extremities |
| Li et al. 2011     | Male, 36, 51          | Painless purple skin papules and plaques on the left arm, anterior chest, and face | -                                                            | Papule on left arm                                                              |
| Gurden et al. 2010 | Male, 63              | Multiple pleomorphic dark red patches and plaques located on the trunk        | Left cervical, left axillary and bilateral inguinal lymph nodes, kidneys, bone marrow | Non-itching pink papules on the head and trunk                                   |
| Eros et al. 2010   | Male, 75              | Generalized erythematous-brown papules, plaques, and tumors on the trunk     | Hepatosplenomegaly, left supraclavicular, both axillary, right inguinal, mediastina, paraaortic lymph nodes, liver, spleen, kidneys, suprarenal glands, bone marrow, brain, stomach, urinary bladder, the rectum, lungs, prostate. | Generalized erythematous-brown papules, plaques, and tumors on the trunk         |
| Female, 69         | Brownish-red, 2-7 cm large cutaneous plaques and tumors on the face and trunk | Inguinal, left cervical, left mesopharyngeal, retroperitoneal, pelvic lymph nodes, bone marrow, CNS | Brownish-red, 2-7 cm large cutaneous plaques and tumors on the face and trunk, cervical and inguinal lymphadenopathy |                                                                                   |
| Fu et al. 2013     | Female, 67            | Small ulcerative lesions on the left calf                                     | Pancytopenia, cervical, mediastinal, axillary, abdominal, inguinal lymph nodes, bones | Dyspnea, fatigue, chest pain, thrombocytopenia, anemia, lymphadenopathy, small ulcerative lesions of the left calf |
| Rakheja et al. 2015 | Female, 69            | Cutaneous nodules                                                             | Bone marrow infiltration, central nervous system, splenomegaly, retroperitoneal adenopathy | Cutaneous nodules                                                               |

Contd...
Table 1: Contd...

| Authors      | Patient’s age, gender | Skin eruption                                                                 | Involving other organs                                                                 | First appearance                                                                 |
|--------------|-----------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Rauh et al. 2012[11] | Male, 78              | -                                                                               | Splenomegaly, retroperitoneal lymphadenopathy, bone marrow, peripheral blood          | Night sweats, weight loss, splenomegaly, retroperitoneal lymphadenopathy, anemia, thrombocytopenia, and leukocytosis |
|              | Male, 82              | -                                                                               | Axillary lymphadenopathy, hepatosplenomegaly, peripheral blood, bone marrow           | Fatigue, recurrent sinus infections, bilateral axillary lymphadenopathy, and hepatosplenomegaly, anemia, thrombocytopenia, and leukocytosis |
|              | Male, 84              | -                                                                               | Kidneys, axillary and inguinal lymphadenopathy, hepatomegaly, peripheral blood, bone marrow | Fatigue, shortness of breath, acute renal failure, bilateral axillary and inguinal lymphadenopathy, and hepatomegaly, pancytopenia |
| Lin et al. 2017[12]  | Male, 86              | Erythematous and violaceous plaques measuring 1.5-5 cm on the scalp and on the back | -                                                                                     | Two erythematous and violaceous plaques measuring 5 cm on the scalp, 1.5-cm nodule on the back |
| Huang et al. 2016[13] | Female, 37           | Solitary well-demarcated violaceous nodule, approximately 4 cm in diameter, with infiltrating erythema surrounding the nodule | Multiple organ failure                                                                 | Single patch on the face |
| Toya et al. 2012[14]  | Male, 45              | Multiple disseminated purpuric nodules over the trunk, the limbs, the face       | Peripheral blood, bone marrow                                                       | Multiple disseminated purpuric nodules over the trunk, the limbs, and the face, neutropenia, anemia |

Table 2: Differential diagnosis between blastic plasmacytoid dendritic cell neoplasm and cutaneous extramedullary myeloid sarcoma, myelomonocytic leukemia

| Marker         | Blastic plasmacytoid dendritic cell neoplasm | Cutaneous extramedullary myeloid sarcoma, myelomonocytic leukemia |
|----------------|---------------------------------------------|------------------------------------------------------------------|
| CD123          | +                                           | -                                                                |
| TLC1           | -                                           | +                                                                |
| CLA            | +                                           | -                                                                |
| CD2AP (CD2-associate protein) | +                                           | -                                                                |
| TLR9, 10       | +                                           | -                                                                |
| BDCA-2         | +                                           | -                                                                |
| MP0            | -                                           | +                                                                |
| CD34           | -                                           | +/-                                                              |

Lymphadenopathy and splenomegaly are observed in 40%–50% and 20% of patients, respectively. Pathological changes in the peripheral blood are found in 60%–90%. Fulminant leukemia typically occurs in the terminal stage of the disease.[3] The central nervous system is involved in the pathological process in isolated cases, one of which is the present case.

The histological picture of BPDCN is characterized by diffuse dermal infiltrate confined around the vessels and appendages of the skin, especially during the early stages. Epidermotropism is rarely observed. In cases where the size of the tumor is large, subcutaneous tissues may be involved.[4,5] Main markers of the disease are CD4, CD56, CD123 without specific markers of B-cells and myelomonocytic cells. Expression of CD4 and CD56 may be weak sometimes. Cells of CD4/CD56 hemodera are characterized by the presence of CD43, HLA-DR, and CD45RA, which are expressed on membranes of B-cells and naive T-lymphocytes.[6] CD123, IL-3 alpha-chain receptor, is a specific marker of BPDCN; however, it is presented on cells in myelomonocytic leukemia. Blood dendritic cell antigen-2 is also a particular marker. T-cell leukemic marker-1 is a regulator of Akt-kinase, lymphoid protooncogene. It is presented on membranes of pDCs and B-cells, and it is absent on mature DC, hematopoietic cells, and T-cells. This marker is typical for early stages of the acute T-cell lymphoblastic leukemia and T-cell prolymphocytic leukemia and finally, for BPDCN.[8]
Cutaneous extramedullary myeloid sarcoma and myelomonocytic leukemia usually mimic BPDCN. There are specific markers to differentiate these pathologies\(^6\) [Table 2].

Extranodal NK/T-cell lymphoma should be excluded before making the diagnosis of BPDCN. This disease is associated with severe course and poor prognosis. Histological findings include angiocentric foci of growth with necrosis. Immunohistochemical phenotype comprises of CD56+, CD3+, TLA1+, granzyme+. Sometimes typical T-cell lymphomas can represent CD56 on the surface of tumor cells. However, T cell receptor (TCR) rearrangement is detected often, and other T-cell markers.\(^{13}\)

**Conclusions**

This clinical case demonstrates the importance of laboratory tests. The first manifestations of the cutaneous lymphoma in our patient were anemia and leukopenia, which can be detected using a routine blood test. When detecting such changes, it is necessary to exclude malignancies and lymphoproliferative disorders. Histological examination helps to clarify a diagnosis of cutaneous lymphoma; however, a specific type of lymphoma needs immunohistochemical analysis.

Cutaneous lymphomas can mimic benign skin dermatoses. In our case, BPDCN mimicked a systemic vasculitis. Only because of the disease progression despite treatment the diagnosis of lymphoma was made. Therefore, it is important to know this entity to be able to recognize it at the early stages.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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