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Case Report

A case of blastic plasmacytoid dendritic cell neoplasm with ecchymotic lesions on the whole body

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Abstract: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) derived from plasmacytoid dendritic cell precursors is a very rare, and characterized by cutaneous and bone marrow involvement and leukemic spread. The neoplasm presents with an aggressive behavior, and the clinical findings include cytopenia, particularly thrombocytopenia. The tumor cells are negative for antigens of T- and B- cell lines. However, these cells express CD4, CD56 and CD123, which are markers of plasmacytoid dendritic cells, and negative for Epstein-Barr virus (EBV). From this point of view, a 71-year-old man who was initially found to have a cutaneous mass on his face and thorax was reported here, and initially was diagnosed as "eczema". The skin rashes then became aggravated on a trial of low dose topical corticosteroid for 2 months. According to skin biopsy, the tumor cells reveal an immature blastic appearance and positive for CD4 and CD56, negative for CD3, CD20, indicating a diagnosis of BPDCN. Here, we report the dismal course of a patient with BPDCN without accepting further therapy, and only survived 3 months.

Keywords: Blastic plasmacytoid dendritic cell neoplasm, BPDCN, neoplasm

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previously known as CD4+/CD56+ hematodermic neoplasm [1] or blastic NK-cell lymphoma [2], is a malignant neoplasm composed of immature hematopoietic cells. In the 2008 World Health Organization (WHO) classification, BPDCN is classified between acute myeloid leukemia (AML) and related precursor neoplasms. Thus, BPDCN is known as a subtype of acute leukemia, and characterized by the clonal proliferation of precursors of plasmacytoid dendritic cells [1, 3, 4]. An asymptomatic patient with a skin lesion is the most frequent clinical manifestation. In recent years, there were many cases reported that this neoplasm frequently detect cutaneous and bone marrow infiltration and leukemic dissemination, and cutaneous tissue lesions generally develop at more than one site. More seriously, as for almost all the cases, the abnormal cells were frequently found in the skin. By immunophenotype, the tumour cell expresses CD4, CD56, CD123 and TDT in the absence of lineage-specific markers of T cells and B-cell or myeloid markers. Initially, many BPDCN patients were often misdiagnosed as the other illness, such as cutaneous lupus erythematosus and eczema. The usual differential diagnosis of BPDCN include nasal-type NK-cell lymphoma, cutaneous T-cell lymphoma, and leukemia cutis [5]. Therapeutically, although BPDCNs initially respond to chemotherapy, they almost always relapse, ultimately undergo leukemic phase, and lead to the patient's death. BPDCN has been reported in any age including the childhood, but predominantly affects elder males, with a sex ratio of 3.3:1, with the median age of affected patients being in the sixth decade of life [6-8]. Below we report a case of advanced BPDCN in an elderly patient.

Materials and methods

The case was from the First University Hospital, Shihezi University School of Medicine. Paraffin-embedded materials were sampled from forma-

Table 1. The manufacturers' protocols and staining intensity for the tested antibodies

Antibody name	Source	Clonality	Clone number	Pretreatment	Dilution	Cellular localization
AE1/3	DAKO	Monoclonal Mouse Anti-Human	34âE12	HIER	1:400	cytoplasmic
CD3	DAKO	Monoclonal Mouse Anti-Human	F7.2.38	HIER	1:50	membranous and cytoplasmic
CD4	Gene Tech	Monoclonal Mouse Anti-Human	1F6	HIER	1:50	membranous
CD20	DAKO	Monoclonal Mouse Anti-Human	M0755	HIER	1:1000	membrane
CD34	DAKO	Monoclonal Mouse Anti-Human	QBEnd/10	HIER	1:400	membranous and cytoplasmic
CD43	Gene Tech	Monoclonal Mouse Anti-Human	DF-T1	HIER	1:600	membranous
CD56	Gene Tech	Monoclonal Mouse Anti-Human	1B6	HIER	1:1200	membranous
CD68	DAKO	Monoclonal Mouse Anti-Human	PG-M1	HIER	1:8000	cytoplasmic
CD79a	DAKO	Monoclonal Mouse Anti-Human	JCB117	HIER	1:800	membranous
CD123	ZSGB-Bio	Monoclonal Mouse Anti-Human	BR4MS	HIER	1:50	membranous and cytoplasmic
CgA	DAKO	Monoclonal Mouse Anti-Human	Nr.M0869	HIER	1:2400	secreted
CK20	DAKO	Monoclonal Mouse Anti-Human	Ks20.8	HIER	1:100	cytoplasmic
Granzyme B	DAKO	Monoclonal Mouse Anti-Human	GrB-7	HIER	1:600	cytoplasmic granule
Ki-67	DAKO	Monoclonal Mouse Anti-Human	M7240	HIER	1:600	nuclear
Lysozyme	DAKO	Polyclonal Rabbit Anti-Human	-----	HIER	1:800	cytoplasmic
MPO	-----	Monoclonal Rabbit Anti-Human	-----	HIER	1:200	cytoplasmic
PAX-5	Gene Tech	Monoclonal Mouse Anti-Human	Sp34	HIER	1:200	nuclear
TdT	Gene Tech	Monoclonal Mouse Anti-Human	SEN28	HIER	1:50	nuclear
TIA-1	GeneTech	Monoclonal Mouse Anti-Human	2G910F5	HIER	1:400	cytoplasmic

HIER, heat-induced epitope retrieval; Gene Tech, Shanghai, China; ZSGB-Bio, Beijing, China; DAKO, Carpentaria, CA.

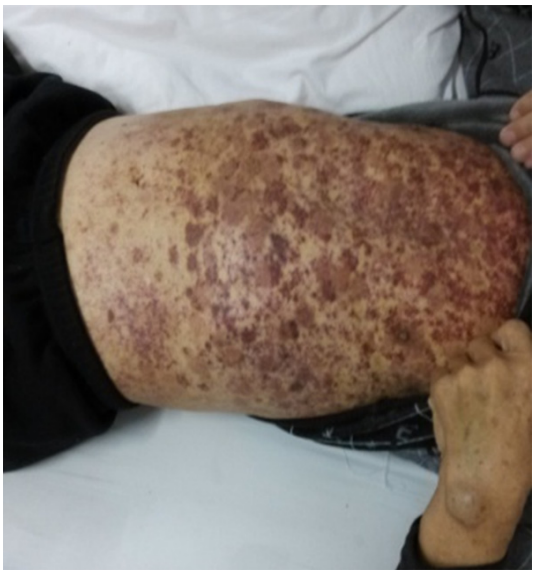

Figure 1. Features of the cutaneous lesions on the thorax and abdomen.

lin-fixed facial and chest lesion. Tissue sections were stained with hematoxylin and eosin for conventional histology. Representative Paraffin-embedded materials sections processed for immunohistochemical studies. Slides were stained according to manufacturers' protocols for the tested antibodies (as shown in **Table 1**).

Results

Clinical features

The clinical features in our patients are summarized. He is a 71-year-old Chinese man who presented with a 2-month history of disseminated, multiple, infiltrated violaceous plaques and nodules on the skin of his face and right of thorax, and measured from 2 to 8 cm in great diameter (**Figure 1**). Subsequently, the plaques were superficially located in the skin of the whole body after a month. It was not pruritic and pain. There was no fever. Physical examination revealed axillary and submandibular lymph nodes were bilaterally palpable. Unfortunately, The initial blood analysis revealed a complete blood count (CBC), which showed a red blood cell count of 2.73×10^{12}, normochromic normocytic anemia (hemoglobin, 85 g/l), thrombocytopenia (32×10^{9}/L). Serological examination disclosed Immunoglobulin A (0.69 g/L), Immunoglobulin M (0.17 g/L), C-3 complement (0.54 g/L), respectively. Other laboratory findings were not significant. Additionally, computed tomography (CT) imaging revealed hepatosplenomegaly (**Figure 2**).

Initially, the patient was treated as "eczema" with topical corticosteroid. Despite topical treat-

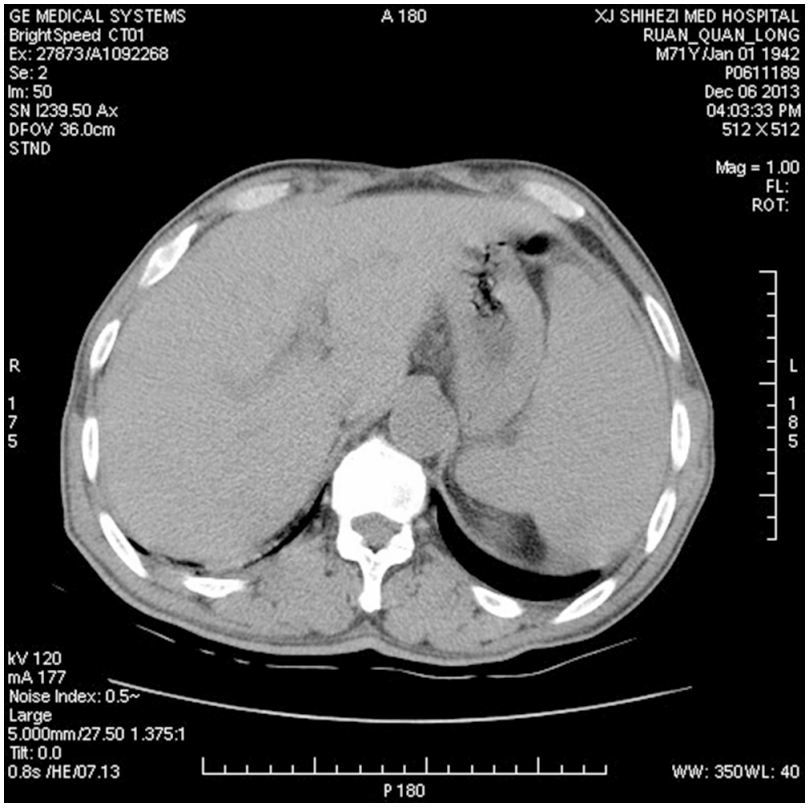

Figure 2. The image of computed tomography (CT). CT revealed hepatosplenomegaly.

ment, no improvement was observed. It eventually grew and spread (**Figure 1**). Subsequently, punch biopsy of skin lesion was performed, indicating a diagnosis of BPDCN. But the patient didn't received special therapy after her first diagnosis. After discussion with her clinicians, the family decided against chemotherapy and chose for palliative care. His blood investigations before abandoning treatment showed the serum levels of hemoglobin and thrombocytopenia were reduced (65 g/l, 26 × 10^9/L, respectively). He passed away there months later of multi-organ failure. He was a farmer, a father of 4 children and lived in Shawan Country of Xinjiang, China.

Histologic findings

The patient was scheduled for biopsy of his skin lesions when was in hospital. A punch biopsy of skin lesion from face and thorax was performed, and the size of biopsy tissue ranged from 0.4 to 0.8 cm in great diameter. The cut surfaces ranged from gray-yellow to gray-red. A biopsy specimen of the facial skin and chest lesion revealed a monomorphic population of mononuclear cells with irregular nuclein, the dermis that was infiltrative of adnexal structures (**Figure 3A**, **3B**). The tumor cells are characterized by a diffuse lymphoid infiltrate of cells with medium sized nuclei and fine chromatin, and showed atrophy of the epidermis, small numbers of necrotic keratinocytes and eosinophilic swelling of the dermal collagen fibers, as well as a perivascular and interstitial lymphohistiocytic infiltration in the entire dermis (**Figure 3C**, **3D**).

Immunohistochemical features

In this case, it could be confused with eczema and the BPDCN could consequently be misdiagnosed because the neoplastic BPDCN cells are similar to blasts that lack lineage-specific markers. Further evaluation is necessary for an accurate diagnosis. Therefore, we performed immunohistochemical staining of the skin biopsy, and immunohistochemical stains revealed that the neoplastic cells were strongly positive for CD4, CD43, CD56, CD123. A few cells showed immunoreactive for TdT (terminal deoxynucleotidyl transferase), CD68, and had a Ki-67 labeling index of 50%, while they are lacking myeloid-related antigens Lysozyme and MPO. Noteworthy, they were also negative for CD3 and CD20, CD79á, which are the markers of T cells and B-cell. They are also devoid of lineage-associated markers such as CK20, AE1/3, CgA, Granzyme B, TIA-1, PAX-5. In addition, Epstein-Barr virus (EBV) was not detected by RNA in situ hybridization, nor were EBV antibodies detected (**Figure 4**). The typical clinical features, histopathology and immunohistological staining result were consistent with the diagnosis of BPDCN [9-11].

Discussion

BPDCN is a rare hematopoietic malignancy. Although pediatric cases have been reported,

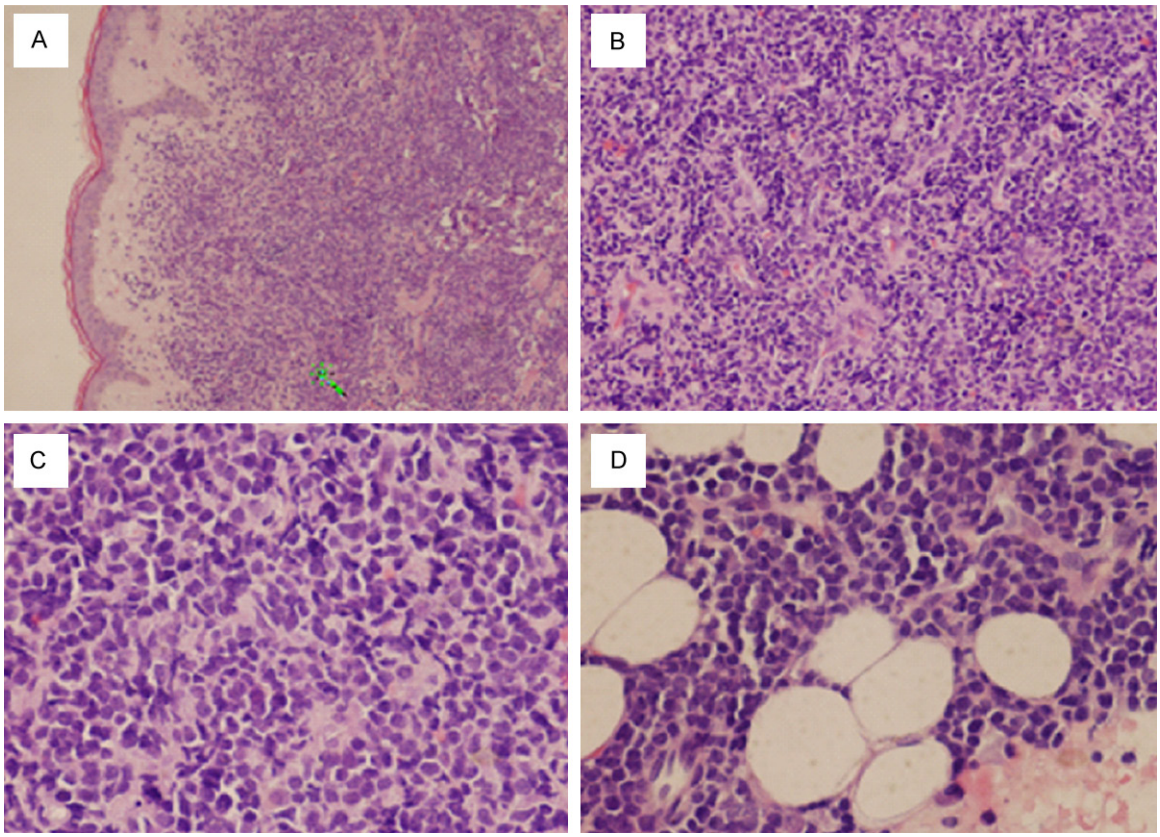

Figure 3. Dermal infiltrate of neoplastic cells. A, B. Shows an extensive diffuse filtration of lymphoid cells (H&E, × 40, × 100). C, D. Medium-sized monomorphous cells with irregular nuclei (H&E, × 200, × 400).

BPDCN occur more commonly in middle-aged or elderly men [6]. The prognosis of BPDCN is also known to be extremely poor. A majority of BPDCN patients usually present with asymptomatic skin nodules and plaques and invariably progress to bone marrow involvement. Simultaneously, lymph node, soft tissue and peripheral blood can be involved [12-15], and leading to the death of patient. Our case was a 71-year-old man, and also characterized by the phenotypic appearance of the cutaneous lesions, and asymptomatic cutaneous lesions initially appeared on his face and right of thorax but subsequently spread to the whole body. Moreover, the axillary and submandibular lymph nodes of our patient showed multiple lymphadenopathies. With the hematologic findings of pancytopenia in our patient, Laboratory data showed there are typically associated with hematologic abnormalities (specifically thrombocytopenia), and there were hepatosplenomegaly. The biopsy of the shin in our patient was also tested which is used to delineate BPDCN from atypical rashes. Thereby, the cases of BPDCN were easily misdiagnosed as eczema or cutaneous lupus erythematosus [16], as prognosis is poor with delay in treatment.

Histopathologically, as seen in the case described, according to skin biopsy and genetic testing, diagnosis can be confirmed. BPDCN was categorized under “AML and related precursor neoplasms” by the 2008 WHO classification, with most cases having been previously classified as blastic natural killer (NK)-cell lymphoma/leukemia or agranular CD4+, CD56+ hematodermic neoplasm [17]. In clinical phenotype, Julia F [18] first distinguish three major different clinical presentations of BPDCN, nodular lesions only, ‘bruise-like’ patches and disseminated lesions (patches and nodules), respectively. The nodular pattern is a more common feature than the originally reported ‘bruise-like’ pattern. Our patient presented demonstrates the disseminated (patches and nodules) lesions presentation of skin. Immunologically, the skin biopsy for our patient stained positive

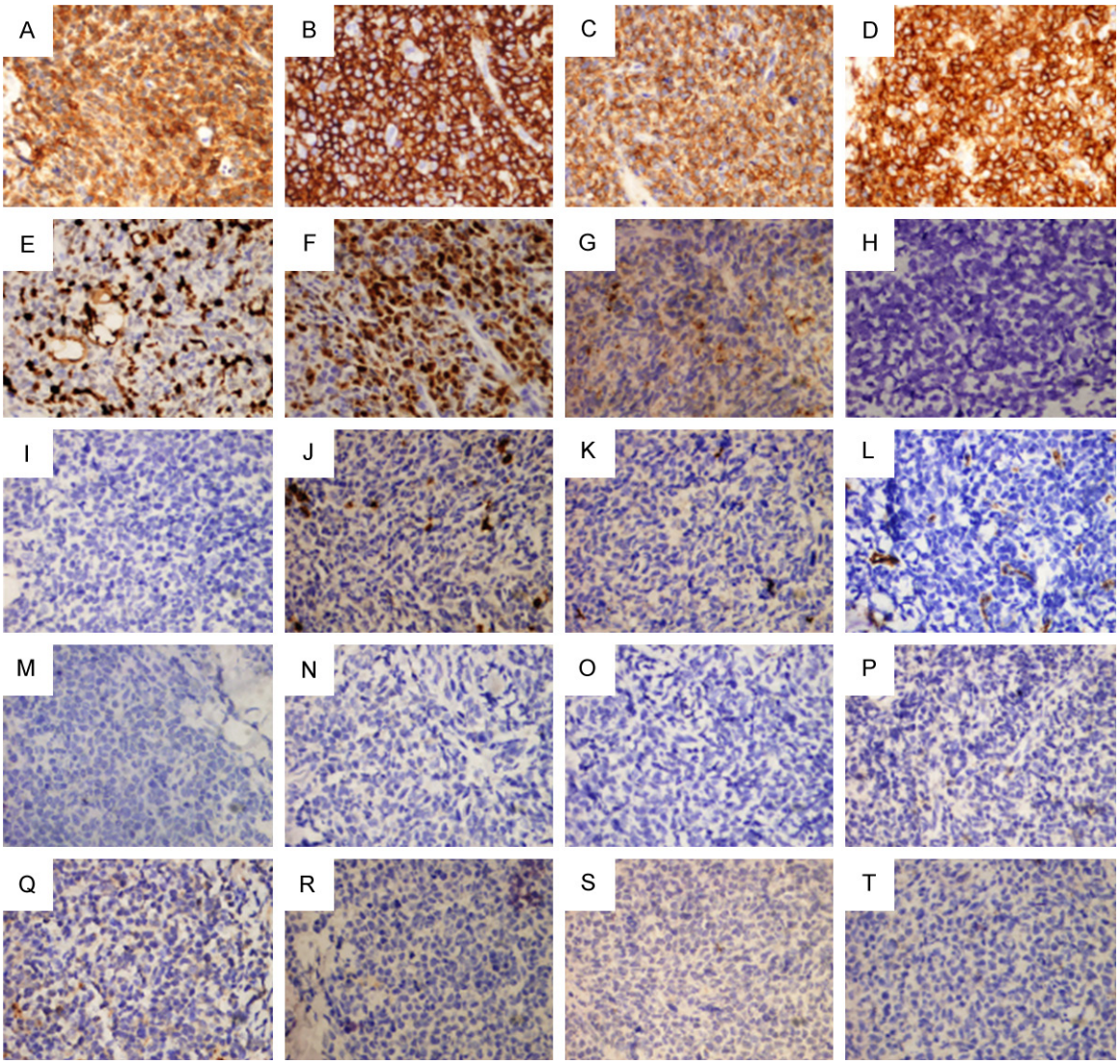

Figure 4. Immunohistochemical detection of cutaneous tumor. A-T: original magnification × 400. A: CD4-positive, B: CD43-positive, C: CD56-positive, D: CD123-positive, E: Ki-67-positive, F: TDT-3-positive, G: CD68-positive, H: Epstein-Barr virus-encoded small RNA (EBER) in situ hybridization-negative. I-T: AE1/3, CD3, CD20, CD34, CD79α, CgA, CK20, Granzyme B, Lysozyme, MPO, PAX-5, TIA-1 are all negative.

for CD4, CD43 and CD56 which usually implicates leukaemia cutis or blastic plasmacytoid cell neoplasm. They also express the plasmacytoid dendritic cell associated (pDC- associated) antigen CD123. But the lineage-specific markers of T cells (CD3) and B-cell (CD20, CD79á) or myeloid markers (Lysozyme and MPO) were all negative. In genetics, Epstein-Barr virus (EBV) was not detected. Thus, immunohistological staining in our patient revealed that it fully meet the diagnostic criteria of BPDCN.

Since this disease entity was first described CD4+/CD56+ hematodermic neoplasm in 1994 [20], several individual cases or small groups of cases of BPDCN have been reported (**Table 2**) [16, 21-26]. As shown in the table, seven cases of BPDCN were collected from the different countries. Of these, the patients' median age was 67 years (36-79 year) and only one patient (14%) was female. More importantly, all of the patients are characterized by nodules, plaques or single or multiple papules. From the **Table 2**, we can see the cutaneous lesions could appeared on the body everywhere. Noteworthily, all of the seven cases expressed CD4 and CD56. We can also know that chemotherapy and radiotherapy are two

Table 2. Clinical Features in 7 Patients with BPDCN

Case NO.	Sex/ Age	Clinical presentations	Initial Location	Size (cm)	CC-D4	CCD-43	CCD-56	CCD-123	Therapy	Follow-up	References
1	M/69	'bruise-like' patches	the chest and left shoulder	NA	+	+	+	+	CVAD andallo-HCT	6 months	[15]
2	M/74	nodular lesions only	left shoulder	5 × 3	+	NA	+	+	low-dose DeVIC and radiation therapy	Sustained complete remission	[16]
3	F/79	disseminated lesions (patches and nodules)	the back	3 × 4	+	NA	+	+	palliative care	8 months	[17]
4	M/74	'bruise-like' patches	the face	NA	+	NA	+	+	palliative chemotherapy with cytarabine and mitoxantrone	4 months	[18]
5	M/67	nodular lesions only	the back	NA	+	+	+	NA	six courses of multidrug chemotherapy consisting of ifosphamide, methotrexed, etoposide, prednisoloneandL-asparaginase,	partial remission	[19]
6	M/36	'bruise-like' patches	the trunk and extremities	NA	+	+	+	NA	prednisone 30 mg/day, radiotherapy and bone marrow transplantation	Sustained complete remission	[20]
7	M/76	nodular lesions only	the face and scalp	7 × 7	+	+	+	+	Six cycles of CHOP	7 months	[21]

Abbreviations: CVAD: hyper-central venous access devices; allo-HCT: allogeneic stem cell transplant; DeVICtherapy: consists of non-multi-drug-resistance (MDR)-associated drugs (dexamethasone ifosphamide, and carboplatin), and etoposide; CHOP: cyclophosphamide, adryamicin, vincristine, and prednisolone. NA: not available.

common treatments, and constantly performed at almost the same time. Conventional chemotherapy alone has not been proven to sustain long-term remission regardless of the therapy used when stem cell transplantation wasn't performed. Due to the limited prospective data of this rare disease, no standard of care treatment has been established for BPDCN. Thus, the prognosis of this disease is extremely poor. Single agent chemotherapy, radiotherapy and polychemotherapy like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high dose methotrexate and high dose cytarabine) has been reported to be necessary to therapy and prognosis of BPDCN. On the other hand, BPDCNs are easy of relapsing, in spite of responding to chemotherapy, they almost ultimately undergo leukemic phase, and lead to the patient's death. In addition, BPDCN frequently occurs in the older patients, the patients often have poor performance status (PS) and renal function. As for our case, the family of our patient decided against chemotherapy and chose palliative care. So the patient we report only survived three months.

Although the diagnostic of BPDCN is basically definite, the etiology is currently unknown. There is a literature [27] which analyzed 14 skin biopsy samples and found that losses of chromosomes 9, 12, 13 and 15 were detected most frequently. These results imply that alterations of the cell-cycle checkpoint controlling proteins p27 (KIP1), p16 (INK4a) and RB1 may exert a profound effect in malignant transformation in BPDCN. On the other hand, BPDCN and Myeloid leukemia cutis (LC) are morphologically indistinguishable malignancies, and frequently manifest in the skin, leading to BPDCN was frequently misdiagnosed, and the delay of therapy. Despite the fact that BPDCN may initially appear as a localized skin tumour, aggressive management including allogeneic bone marrow transplantation should be considered immediately, as it is currently the only option associated with long-term survival. Relapse frequently occurs within 6 months or less from the initiation of chemotherapy and most patients experience rapid progression that is refractory to conventional chemotherapy. Due to no standard of care treatment has been established for BPDCN. The prognosis of patients with BPDCN is poor, with a median survival of 12-14 months regardless of treatment type [28]. Relapse frequently occurs in this disease, and rapid progression of the disease is typical.

We stress the importance of this case because that BPDCN should be considered in the differential diagnosis of skin rashes. Although clarification of the immunophenotypic features of BPDCN has improved its recognition, this entity remains a diagnostic challenge. Cutaneous lesions are usually the only sign of the disease. Thereby, repeated skin biopsy and bone marrow examination should be performed in every case of BPDCN, and dermatologists should be knowledgeable about it and play a crucial role in uncovering this malignancy and avoiding diagnostic delays. On the other hand, further studies are needed to define the molecular pathogenesis and biologic markers that aid in the diagnosis of BPDCN. Furthermore, clinical trials and/or multi-institutional cooperation are necessary to define the optimal therapeutic strategies that will lead to better outcomes in patients with this uncommon group of disorders.

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Disclosure of conflict of interest

No potential conflicts of interest relevant to this review were reported.

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