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CASE REPORT

Bruise-like cutaneous lesions as the early presentation of blastic plasmacytoid dendritic cell neoplasm

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ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a very rare and highly aggressive hematopoietic malignancy associated with a poor prognosis. It has been recognized to originate from precursors of plasmacytoid dendritic cells and has recently been established as a distinct entity. The most frequent clinical presentations are prominent skin lesions, followed by peripheral blood, bone marrow, and other organ involvement. Treatment outcomes are often disappointing due to a high relapse rate after chemotherapy and risk of leukemic dissemination. Herein, we report a case of BPDCN in a 41-year-old man who presented with cutaneous and nasopharyngeal lesions, and achieved a complete response after systemic chemotherapy. Dermatologists should be aware of BPDCN and its clinical presentations, as early diagnosis with appropriate treatment is crucial to improve its prognosis.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previous known as blastic natural-killer (NK) cell lymphoma and CD4+/CD56+ hematodermic neoplasm, is a rare and aggressive hematopoietic malignancy with prominent cutaneous involvement and high risk of leukemic disseminations.[1–3] NK cells were previously regarded as the cells of origin of this neoplasm due to the high expression levels of CD56 in patients with CD4+ cutaneous lymphoma and a distinct blastic cytology.[4] However, the lack of other NK-lineage markers, absence of Epstein–Barr virus (EBV) infection, and CD4 expression were not typical of NK cell development in most cases. Therefore, the true NK cell derivation of this tumor was considered controversial.[5] Subsequent studies involving immunophenotypic and functional analyses have shown that the tumor cells are more likely to be derived from precursors of plasmacytoid dendritic cells (pDCs).[6–8] Therefore, BPDCN is regarded as a distinct entity and was categorized among "acute myeloid leukemia and related precursor neoplasm" by the World Health Organization in 2008.[9]

We herein report a case of BPDCN with multiple bruise-like skin lesions on the trunk and face at initial presentation.

Case report

A 41-year-old male patient presented with a 1-month history of multiple asymptomatic bruise-like lesions on his trunk and face. Additionally, he developed ecchymotic lesions on the trunk easily from scratching. He also suffered from several episodes of bleeding in the right nasal cavity for 1–2 months. He denied having any underlying systemic disease or malignancy, except for undergoing a cholecystectomy 1 year earlier. On physical examination, we noted multiple 2–3 cm in diameter bluish to violaceous infiltrated patches or plaques scattered on his trunk and a few irregularly shaped violaceous plaques on his cheeks (Figure 1). There was neither palpable cervical, axillary, or inguinal superficial lymphadenopathy nor hepatosplenomegaly. He did not experience any episodes of fever, night sweating, or weight loss during this period.

Skin biopsy from his chest revealed diffuse interstitial, perivascular, and periadnexal infiltrations of monotonous medium-sized blastic cells with slightly irregularly shaped nuclei and fine

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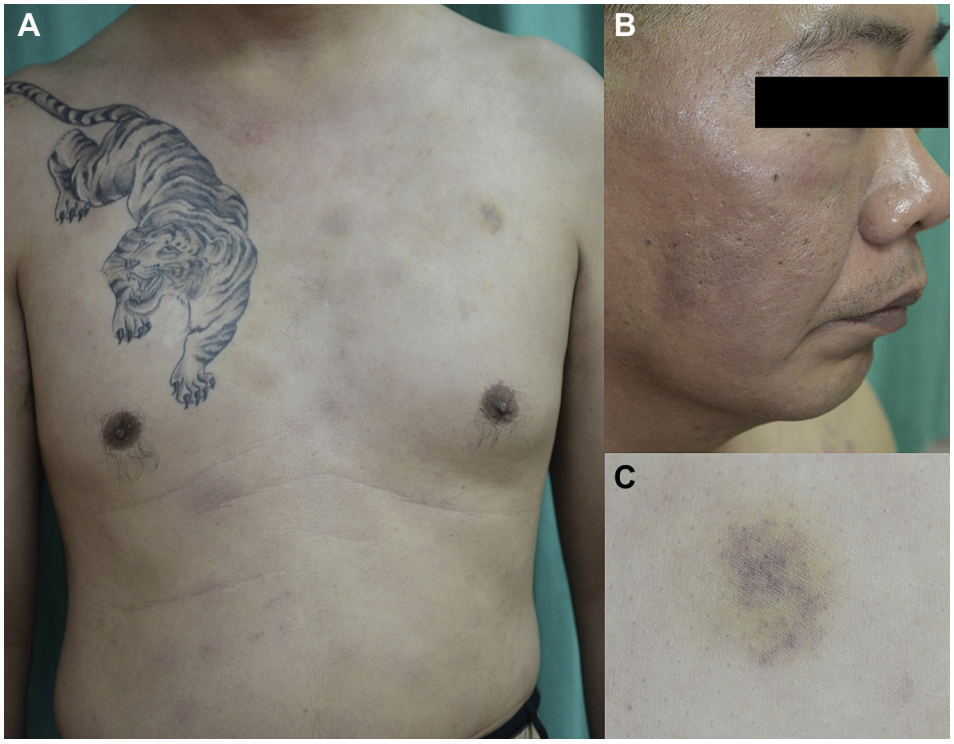

Figure 1 (A, B) Multiple bruise-like or violaceous infiltrated patches and plaques on the trunk and face. (C) Close-up view of the bruise-like plaque on the chest.

chromatin in the dermis. The epidermis was spared with a grenz zone. Neither angiocentrism nor necrosis was present. Erythrocytes extravasation and a few mitotic figures were also present (Figure 2). On immunohistochemical staining, tumor cells were positive for CD4, CD56, and leukocyte common antigen (CD45), and negative for CD3, CD20, CD30, CD45RO, lambda/kappa light chain, epithelial membrane antigen, pancytokeratin (AE1/AE3), and myeloperoxidase. In addition, the tumor cells were also positive for CD123 (Figure 3). *In situ* hybridization for EBV-encoded small nuclear RNA was negative. A biopsy from his right nasopharyngeal tissue also revealed infiltration of diffuse medium-sized lymphoid cells that were positive for CD4, CD56, and CD123 (Figure 4), and negative for CD3 and EBV-encoded small nuclear RNA.

Laboratory examination showed a normal complete blood cell count with no leukocytosis and no thrombocytopenia. The biochemistry profile, including electrolytes, lactic dehydrogenase, alkaline phosphatase, antinuclear antibody, hepatic and renal function tests, coagulation profile, and urine analysis, was all within normal ranges.

Serology tests for human immunodeficiency virus, rapid plasma regain, hepatitis A/B/C viruses, and human T-cell leukemia virus type I showed negative results. Chest X-ray and cardiac echo revealed no abnormalities. Peripheral blood smear and bone marrow biopsy revealed no conspicuous neoplastic cell infiltrations. Whole body computed tomography revealed thickened soft tissue in his nasopharyngeal mucosa and in both pharyngeal tonsils with no conspicuous lymphadenopathy and no definite distant metastasis.

Based on the typical clinical features, histopathology, and immunohistochemical studies, a diagnosis of BPDCN with skin and nasopharynx involvement was made. The patient was then referred to the hemato-oncology ward to undergo CHOP treatment

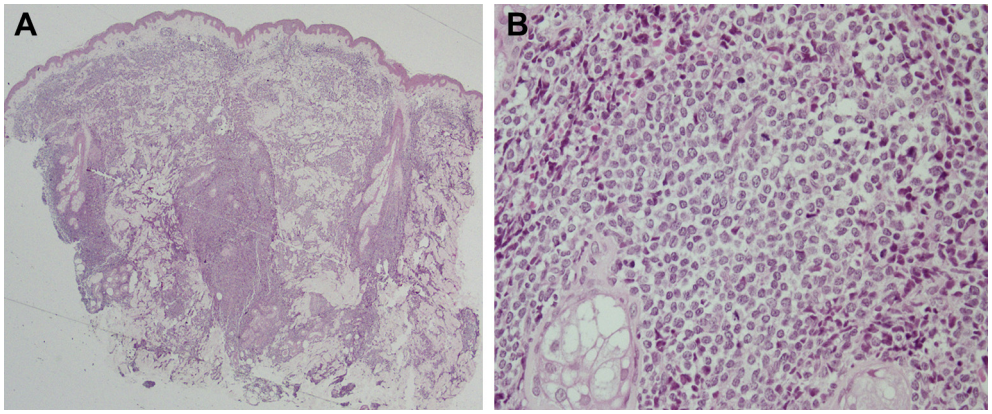

Figure 2 Skin biopsy from the chest. (A) Diffuse interstitial, perivascular, and periadnexal infiltration of lymphoblastic-like cells in the dermis and subcutaneous tissue. The epidermis is spared with a grenz zone. Neither angiocentrism nor necrosis is present (hematoxylin and eosin, 1.25×). (B) Monotonous medium-sized blastic cells with irregularly shaped nuclei and fine chromatin in the periadnexal area. Mitotic figures are occasionally observed (hematoxylin and eosin, 400×).

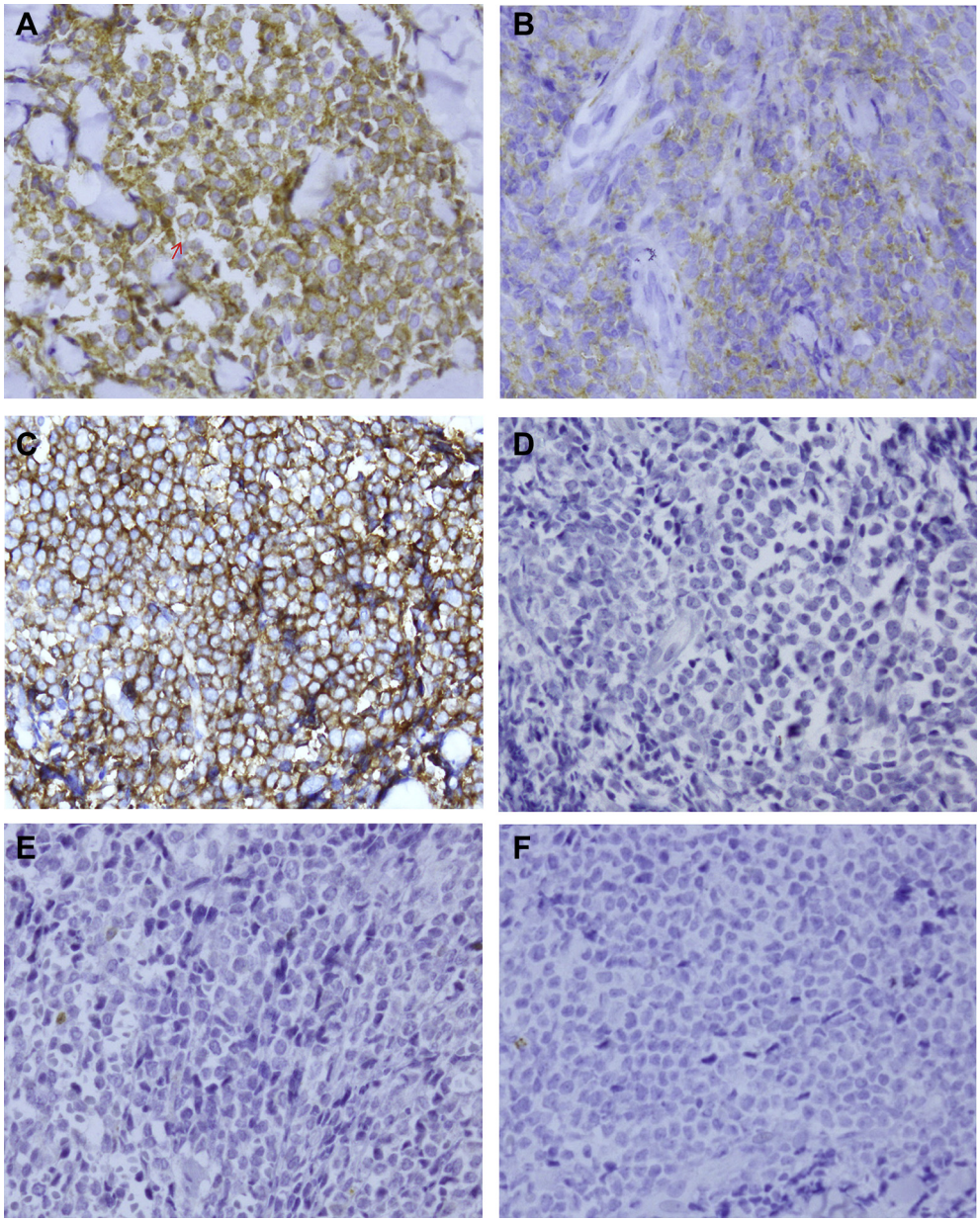

Figure 3 Immunohistological staining results of skin biopsy are positive for (A) CD4 with dendritic cytoplasmic staining (arrow), (B) CD56, and (C) CD123, and negative for (D) myeloperoxidase, (E) CD3, and (F) CD20. All images are at their original magnification (400×).

(cyclophosphamide, doxorubicin, vincristine, and prednisolone) for 3 weeks for a total of eight cycles. After two cycles of CHOP, the bleeding tendency from his nasal cavity stopped. A complete response was achieved after chemotherapy, and the bruise-like infiltrated patches and plaques regressed (Figure 5A and B). The occurrence of ecchymosis on his body from scratching also diminished during treatment (Figure 5C). Follow-up positron emission tomography–computed tomography examination revealed no other extracutaneous organ involvement. Finally, the patient was regularly followed-up in our hematology outpatient clinic, and received maintenance therapy of cyclophosphamide and prednisolone.

Discussion

In 1994, Adachi et al[4] described the first case of BPDCN in a Japanese male with cutaneous CD4+ lymphoma. Since then, Petrella et al[2] and other groups[3] have reported additional cases and re-characterized the immunophenotypic and histological features of BPDCN. The nomenclature of such CD4+/CD56+ neoplasms has been continuously evolving due to uncertainties regarding their true histogenesis. Further advanced research came with the delineation of the pDCs by Grouard et al[10], and the expression of CD123 (IL-3 receptor α chain) of lymphoid cells by Lúcio et al.[6] Subsequent studies revealed that many features that are common in phenotypic and functional characterization between both pDCs and CD4+/CD56+ neoplasms, suggesting that the neoplasm was derived or originated from precursors of pDCs.[7]

BPDCN is very rare, accounting for less than 1% of all acute leukemia[8] and 0.7% of cutaneous lymphomas.[11] According to 2008 and 2009 annual reports from the Taiwan Cancer Registry, the incidence of BPDCN is approximately 3–6 persons/year. There are fewer than 250 cases described in the literature to date[12,13], and there are only a few reports of Taiwanese cases.[13,14]

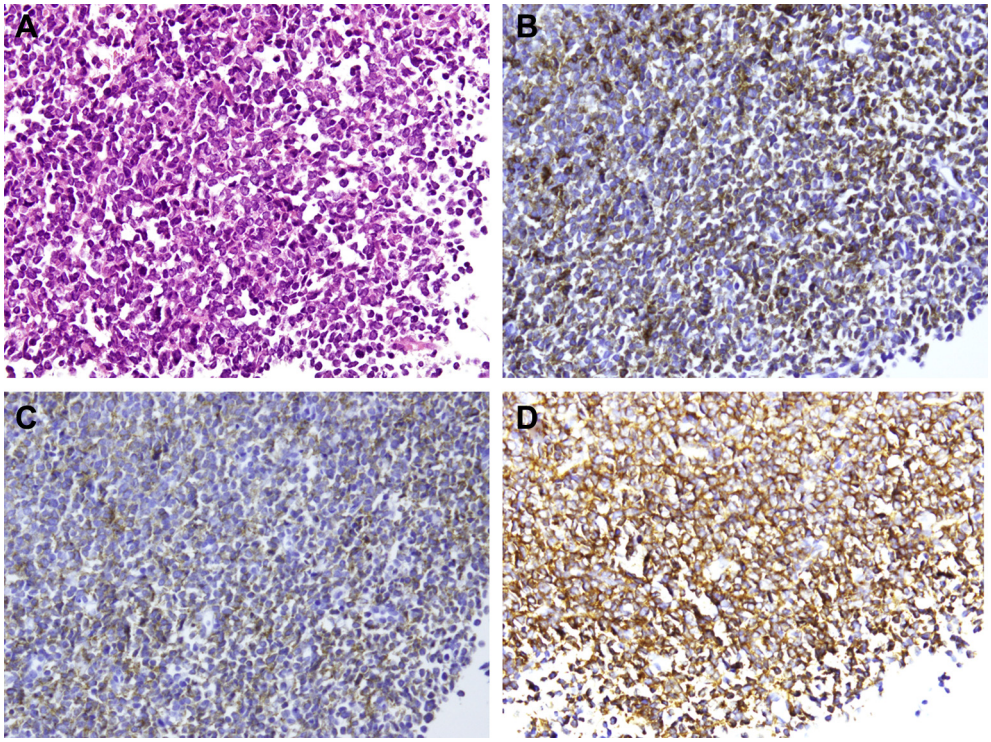

Figure 4 Nasopharyngeal biopsy from the right nasal cavity. (A) Diffuse medium-sized lymphoid cell infiltration (hematoxylin and eosin, 400×). (B–D) Immunohistological staining results of the nasopharyngeal soft tissue are positive for (B) CD4, (C) CD56, and (D) CD123. All images are at their original magnification (400×).

The disease mainly affects middle-aged and elderly men (male/female ratio of 3:1); however, rare congenital and pediatric cases have also been reported.[14,15] The mean age is 55 years at diagnosis (ranging from 3 days to 96 years), and 76% of the patients are older than 50 years.[16]

Skin lesions are the most common manifestation in nearly all BPDCN patients. However, a few cases of patients initially presenting with fulminant leukemia but lacking cutaneous lesions have been reported.[17] Bone marrow and/or peripheral blood and lymph node involvement occurred in 60–90% and 40–50% of patients, respectively. Initial fulminant leukemia is less common (5–20%), but the risk of leukemic dissemination when tumor progression or relapse is greater and is nearly always present in the terminal stage of BPDCN. According to the literature review, more than half of the patients had only cutaneous lesions at the time of diagnosis.[3]

The cutaneous manifestation of BPDCN can be either localized or wide spread. Their appearance is variable and includes violaceous, erythematous, red brown and/or purpuric patches, plaques, nodules, and ulcerative lesions on the head, trunk, and extremities.[9,18] The bruise-like infiltrated lesions, as observed in our case, could be the early manifestation of neoplastic cell infiltration with red blood cell extravasation in the skin.

The invasion of other mucosal sites is relatively infrequent (about 10%).[1] Other organs, such as the liver, spleen, nasopharynx, tonsils, kidneys, and central nervous system have also been reported to be involved in BPDCN. Systemic B symptoms are rare at diagnosis.[7] Few cases of BPDCN with nasopharyngeal lesions denoted in the literature are often accompanied with lymph node or blood involvement.[3,19] However, our case showed both skin and nasopharynx involvement, and no conspicuous systemic dissemination. Such clinical manifestations were rarely noted in the literature. This could be explained by the early diagnosis after a 1-month period of skin and nasal manifestations in our case.

Histologically, BPDCN shows diffuse monotonous infiltrates of medium-sized lymphoblastoid cells with round-to-oval nuclei, indistinct nucleoli, scanty cytoplasm, and finely dispersed chromatin, which resemble lymphoblasts or myeloblasts in the dermis and sometimes the subcutis. There is generally no epidermotropism, necrosis, or angioinvasion. The neoplastic cells are often positive for CD4, CD56, CD43, and cutaneous lymphocyte-associated antigen (CLA).[20] Expression levels of terminal deoxynucleotidyl transferase, CD33, CD68, and CD45RA are variable.[3] These neoplastic cells also express the pDC associated antigens CD123, BDCA-2/CD303, and TCL-1, and are negative for common T-cell, B-cell, and myeloid cell lineage markers.[1] It should be noted that some CD4− or CD56− variants have been described for BPDCN.[21] The T-cell receptor gene is germline and rearrangement is nonclonal. It should be differentiated from other blastic hematopoietic malignancies demonstrating positive of CD56 and CD4.[19] The distinction of cases of acute myeloid leukemia/myeloid sarcoma that are CD4+/CD56+ is difficult. The tumors often express multiple myeloid markers such as myeloperoxidase exclusively, whereas only minorities of them are weakly positive of CD123.[22] Therefore, detection of multiple myeloid markers other than CD33 favors the diagnosis of acute myeloid leukemia/myeloid sarcoma, whereas expression of multiple plasmacytoid dendritic cell markers favors BPDCN. Extranodal NK/T-cell lymphoma, nasal type is histologically associated with angioinvasion of tumor cells, EBV infection, and the absence of CD123 expression. Myeloid neoplasms with increased pDCs acumination at nodal or extranodal sites often lack CD56 expression and are morphologically mature. In our case, the coexpression of CD4, CD56, and CD123 and lack of EBV infection in the nasal mucosa helped us to clarify whether there is merely an increase in pDC infiltrates in response to immune activation as well as in reactive lymphoid hyperplasia,[7] and to rule out nasal type NK/T-cell lymphoma.

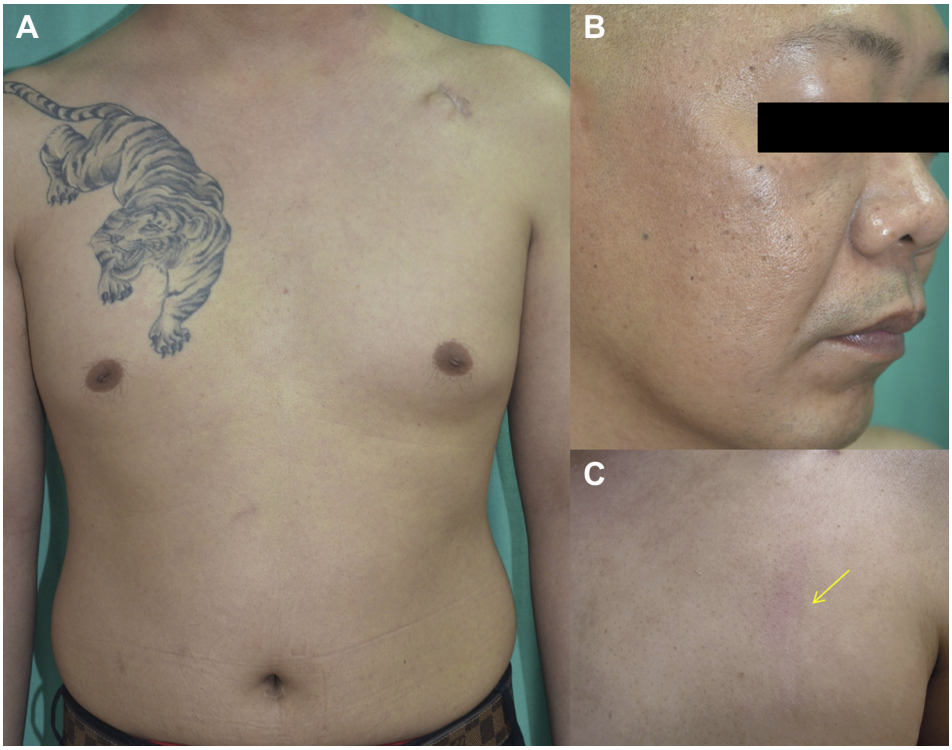

Figure 5 Complete response after chemotherapy. (A, B) The bruise-like and violaceous infiltrated lesions on the trunk and face are diminished. (C) No appearance of ecchymosis on the trunk after scratching (arrow).

The overall prognosis of BPDCN is dismal. The median survival is approximately 12–14 months, and the 5-year-survival rate is 0–6%.[23] The initial clinical presentation of BPDCN may seem deceptively indolent and often responds to multiagent chemotherapy. However, relapse with rapid extracutaneous dissemination, with or without leukemia, occurs in the vast majority of patients with an average disease-free time of 9–11 months.[1] Reports of efficacy of treatments in patients with BPDCN indicate that acute lymphoblastic leukemia/lymphoma-type therapy results in a better outcome than acute myeloid leukemia-type therapy, despite a closer relationship between pDCs and myeloid cells.[24] Long lasting remissions or curable cases have been rarely reported in pediatric patients and younger patients who received aggressive acute leukemia type therapy and allogeneic stem cell transplantation.[15,25] A multivariate analysis from Bekkenk et al[23] also revealed that an age <40 years, high expression of deoxynucleotidyl transferase, presentation of only cutaneous lesions, and aggressive treatment using an acute leukemia protocol are associated with a more favorable prognosis.

Our BPDCN case presented with early cutaneous manifestations, including bruise-like lesions, which were accompanied by unusual nasopharyngeal involvement. Although a complete response was observed after initial chemotherapy with regression of nasal and skin lesions, long-term follow-up is necessary due to the high relapse rate, rapid leukemic dissemination, and poor prognosis of the disease. Cutaneous lesions are often the first prominent presentation of BPDCN and show a great variability in their morphologic and phenotypic features.[18] The diagnosis of BPDCN requires exhaustive examination by expert clinicians and histopathologists. Dermatologists should be aware of the clinical presentations of such hematopoietic neoplasms because the early diagnosis of the disease and appropriate treatment is important to improve the outcome.

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**:687–700.
2. Petrella T, Comeau MR, Maynadié M, et al. 'Agranular CD4+ CD56+ hematodermic neoplasm' (blastic NK-cell lymphoma) originates from a population of CD56+ precursor cells related to plasmacytoid monocytes. *Am J Surg Pathol* 2002;**26**:852–62.
3. Petrella T, Bagot M, Willemze R, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol* 2005;**123**:662–75.
4. Adachi M, Maeda K, Takekawa M, et al. High expression of CD56 (N-CAM) in a patient with cutaneous CD4-positive lymphoma. *Am J Hematol* 1994;**47**:278–82.
5. Petrella T, Dalac S, Maynadie M, et al. CD4+ CD56+ cutaneous neoplasms: a distinct hematological entity? Groupe Francais d'Etude des Lymphomes Cutanes (GFELC). *Am J Surg Pathol* 1999;**23**:137–46.
6. Lúcio P, Parreira A, Orfao A. CD123hi dendritic cell lymphoma: an unusual case of non-Hodgkin lymphoma. *Ann Intern Med* 1999;**131**:549–50.
7. Jegalian AG, Facchetti F, Jaffe ES. Plasmacytoid dendritic cells: physiologic roles and pathologic states. *Adv Anat Pathol* 2009;**16**:392–404.
8. Jacob MC, Chaperot L, Mossuz P, et al. CD4+ CD56+ lineage negative malignancies: a new entity developed from malignant early plasmacytoid dendritic cells. *Haematologica* 2003;**88**:941–55.
9. Facchetti FJD, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: Swerdlow SH, Campo E, Hazzis NL, editors. *WHO classification of tumors of hematopoietic and lymphoid tissues*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2008. p. 145–7.
10. Grouard G, Rissoan MC, Filgueira L, Durand I, Banchereau J, Liu YJ. The enigmatic plasmacytoid T cells develop into dendritic cells with interleukin (IL)-3 and CD40-ligand. *J Exp Med* 1997;**185**:1101–11.
11. Ng AP, Lade S, Rutherford T, McCormack C, Prince HM, Westerman DA. Primary cutaneous CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma): a report of five cases. *Haematologica* 2006;**91**:143–4.
12. Borchiellini D, Ghibaudo N, Mounier N, et al. Blastic plasmacytoid dendritic cell neoplasm: a report of four cases and review of the literature. *J Eur Acad Dermatol Venereol* 2012;**27**:1176–81.
13. Liao JB, Chuang SS, Chen HC, Tseng HH, Wang JS, Hsieh PP. Clinicopathologic analysis of cutaneous lymphoma in Taiwan: a high frequency of extranodal natural killer/t-cell lymphoma, nasal type, with an extremely poor prognosis. *Arch Pathol Lab Med* 2010;**134**:996–1002.
14. Yang CS, Wang J, Chang TK. Congenital blastic plasmacytoid dendritic cell neoplasm. *Pediatr Blood Cancer* 2012;**58**:109–10.
15. Jegalian AG, Buxbaum NP, Facchetti F, et al. Blastic plasmacytoid dendritic cell neoplasm in children: diagnostic features and clinical implications. *Haematologica* 2010;**95**:1873–9.

16. Li Y, Li Z, Lin HL, Chen XH, Li B. Primary cutaneous blastic plasmacytoid dendritic cell neoplasm without extracutaneous manifestation: case report and review of the literature. *Pathol Res Pract* 2011;**207**:55–9.
17. Rauh MJ, Rahman F, Good D, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation, lacking cutaneous involvement: case series and literature review. *Leuk Res* 2012;**36**:81–6.
18. Cota C, Vale E, Viana I, et al. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm-morphologic and phenotypic variability in a series of 33 patients. *Am J Surg Pathol* 2010;**34**:75–87.
19. Magro CM, Porcu P, Schaefer J, et al. Cutaneous CD4+ CD56+ hematologic malignancies. *J Am Acad Dermatol* 2010;**63**:292–308.
20. Petrella T, Meijer CJ, Dalac S, et al. TCL1 and CLA expression in agranular CD4/CD56 hematodermic neoplasms (blastic NK-cell lymphomas) and leukemia cutis. *Am J Clin Pathol* 2004;**122**:307–13.
21. Bénet C, Gomez A, Aguilar C, et al. Histologic and immunohistologic characterization of skin localization of myeloid disorders: a study of 173 cases. *Am J Clin Pathol* 2011;**135**:278–90.
22. Cronin DM, George TI, Reichard KK, Sundram UN. Immunophenotypic analysis of myeloperoxidase-negative leukemia cutis and blastic plasmacytoid dendritic cell neoplasm. *Am J Clin Pathol* 2012;**137**:367–76.
23. Bekkenk MW, Jansen PM, Meijer CJ, Willemze R. CD56+ hematological neoplasms presenting in the skin: a retrospective analysis of 23 new cases and 130 cases from the literature. *Ann Oncol* 2004;**15**:1097–108.
24. Pagano L, Valentini CG, Pulsoni A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. *Haematologica* 2013;**98**:239–46.
25. Dalle S, Beylot-Barry M, Bagot M, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? *Br J Dermatol* 2010;**162**:74–9.