Med Oncol (2012) 29:2417–2422
DOI 10.1007/s12032-012-0215-y

CASE REPORT

Cutaneous blastic plasmacytoid dendritic cell neoplasm occurring after spontaneous remission of acute myeloid leukemia: a case report and review of literature

Wanzhuo Xie · Yanmin Zhao · Ling Cao · Weijia Huang · Yanli Wang · He Huang

Received: 22 February 2012 / Accepted: 10 March 2012 / Published online: 3 April 2012
© Springer Science+Business Media, LLC 2012

Abstract Spontaneous remission of acute myeloid leukemia (AML) is an extremely uncommon event. The etiology is associated with infection, blood transfusion or granulocyte colony-stimulating factor therapy, which trigger immune responses to exert an antileukemic effect. The remission is usually temporary and followed by rapid relapse. However, we present a case of a 42-year-old man with spontaneous remission of AML-M5a, who did not relapse but developed a rare and aggressive lymphoma, named cutaneous blastic plasmacytoid dendritic cell neoplasm (BPDCN). The neoplasm cells are positive for CD4, CD56, CD43, CD45, and CD123, but negative for other lineage-specific markers. To our knowledge, this is the first report of BPDCN occurring after spontaneous remission of AML, although it has been observed that some BPDCN could shift to myeloid leukemia. Occurrence of the two diseases is more than a coincidence. Discovery of such cases may shed further light on the inner connection between BPDCN and myeloid disorders.

Keywords Spontaneous remission · Acute myeloid leukemia · Plasmacytoid dendritic cells · Neoplasm

Introduction

Spontaneous remission (SR) of acute myeloid leukemia (AML) in the adult is an uncommon phenomenon and usually temporary. The majority of the reported cases of spontaneous remission relapsed after 1–36 months with a mean duration of remission around 7.7 months [1]. However, we report a patient with spontaneous remission of AML, who did not relapse but developed an exceedingly rare lymphoma, named CD4+/CD56+ blastic plasmacytoid dendritic cell neoplasm. Herein, a detailed review of the literature on such remission is given and the relationship between the two diseases is discussed.

W. Xie · Y. Zhao (✉) · L. Cao · W. Huang · Y. Wang · H. Huang
Bone Marrow Transplantation Center, The First Affiliated Hospital of Zhejiang University, 79 Qingchun Road, Hangzhou 310003, China
e-mail: zjzhaoyanmin@163.com

Case report

A 42-year-old male patient was admitted to our hospital in September 2008, with fever of 40 °C, repeated fatigue and dizziness. No liver or spleen enlargement, lymphadenopathy or signs of bleeding were found. Upon admission, the blood routine showed pancytopenia: white blood cell (WBC) count, 500/μL, with 27.5 % neutrophils; hemoglobin level, 6.8 g/dL; and platelet count, 93,000/μL. Biochemistry tests noted elevations in serum lactate dehydrogenase (LDH), 336 U/L (normal range <250 U/L); ferritin, 6,245.0 ng/mL (normal range 7.0–323.0 ng/mL); and C reactive protein, 43.10 mg/L (normal range <5 mg/L). Both urinary lambda and kappa light chains were elevated, with a normal urinary kappa/lambda ratio (46.40 mg/dL: 39.00 mg/dL). Serum and urine protein electrophoresis with immunofixation were also within normal limits. An ultrasound of the abdomen was normal, and chest CT scan showed consolidative patches in bilateral lower lobes and localized pleural thickening. Marrow aspirate was hypercellular, containing 91.5 % large blast cells, which had folded nuclei with fine chromatin and inconspicuous nucleoli (Fig. 1a). Blasts were weakly positive for peroxidase (POX) and Sudan black (SB), and strongly positive

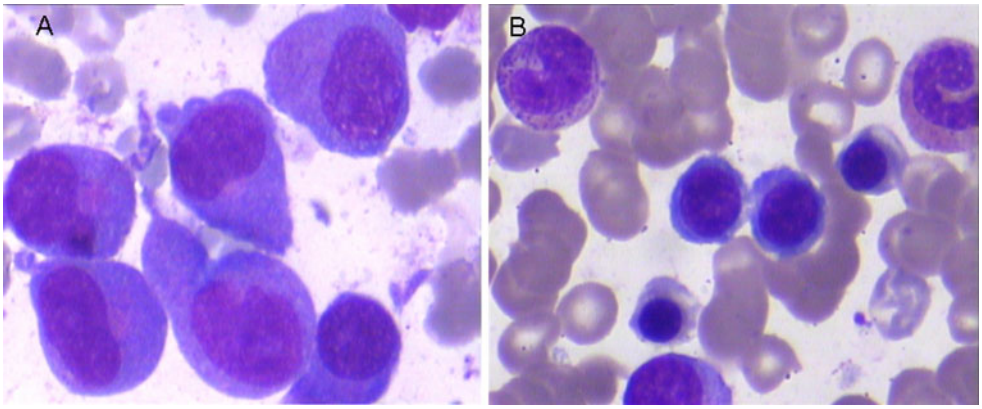

Fig. 1 Cytology of bone marrow cells (Wright stain, ×1,000). **a** Bone marrow was packed with large blast cells, which had folded nuclei with fine chromatin and inconspicuous nucleoli. The percentage of blast cells amounted to 91.5 %. **b** Bone marrow smear showed normocellularity and remission of AML without blasts

for non-specific esterase (NSE) staining with inhibition of the reaction by NAF, consistent with AML-M5a by the FAB criteria. Cytogenetic studies revealed a normal karyotype. Flow cytometry showed the blasts were positive for CD33, CD64, CD56, CD65s, and CD38, and negative for CD117, CD34, CD14, CD11b, and CD138. Thus, the diagnosis of acute monocytic leukemia was established. Inductive chemotherapy was withheld as a result of the patient's active infection of pneumonia. Antibiotics were administered intravenously starting with Cefepime and continued with Imipenem and Fluconazole. Granulocyte colony-stimulating factor (G-CSF) was administered to correcting leukopenia.

Twelve days after admission, the hemoglobin unexpectedly began to improve with gradually rising levels of leukocyte, concomitant with improvement in the clinical condition and resolution of fever. A follow-up bone marrow study 2 weeks after the initial diagnosis of AML showed a hypocellular marrow with adequate megakaryocytes and absence of leukemic blasts. Re-evaluation by bone marrow aspiration 4 weeks later revealed normocellularity and remission of AML without blasts in the bone marrow (Fig. 1b). Flow cytometry of marrow aspirate showed that <0.07 % of the gated mononuclear cells had similar cell surface markers previously demonstrated on the leukemic cells. Thus, the patient was in complete spontaneous remission and subsequently discharged home. During follow-up for more than 24 months, his clinical condition was stable and his blood cell counts were normal.

In December 2010, the patient was presented with painless multicentric cutaneous lesions on the trunk. On admission, these lesions gradually increased in size and presented as dusky erythematous nodules of approximately 3 cm in diameter (Fig. 2a). The laboratory results, including blood cell counts were within the normal range. The antinuclear antibody was negative. Skin biopsy revealed lymphoid infiltration of the dermis, consisting of medium-sized monomorphic blast cells. Immunostaining showed the neoplastic cells were positive for CD4, CD56, CD43,CD45, and CD123, but negative for CD3, CD5, CD20, CD33, CD68, myeloperoxidase (MPO), and BCL2 (Fig. 2b–e). EBV detection was negative. According to the criteria of the WHO classification, the patient was diagnosed as having a CD4+/CD56+ blastic plasmacytoid dendritic cell neoplasm (BPDCN). The bone marrow biopsy, computed tomography of mediastinum, and ultrasonography of abdomen showed no evidence of extracutaneous involvement. Flow cytometry of marrow aspirate showed 1.25 % of immature lymphocyte were present and positive for CD20, CD10, CD19, sIgM, and HLA-DR, indicating reactive proliferation of lymphocytes. The patient received two cycles of CHOP regimen and achieved complete remission. Now, he was introduced to our transplantation department for further treatment.

Discussion

Spontaneous remission is rare in the adult with AML and often lasting for a short duration. Literature review through PUBMED since 1980 revealed more than 30 cases of spontaneous remission of AML, and 10 cases that were acute monocytic leukemia (AML-M5), as well as this case, were summarized in Table 1. The median age of these 11 patients was 47 years (range 28–83 years) old. Eight cases have a short-time SR (mean 5, range 0.5–14 months), followed by relapse of leukemia and subsequent progression. However, long-term remissions have also been documented in three cases.

The mechanism inducing SR is not well established. Similar to this case, SR often occurred after severe infections, such as pneumonia [1] and sepsis with group G

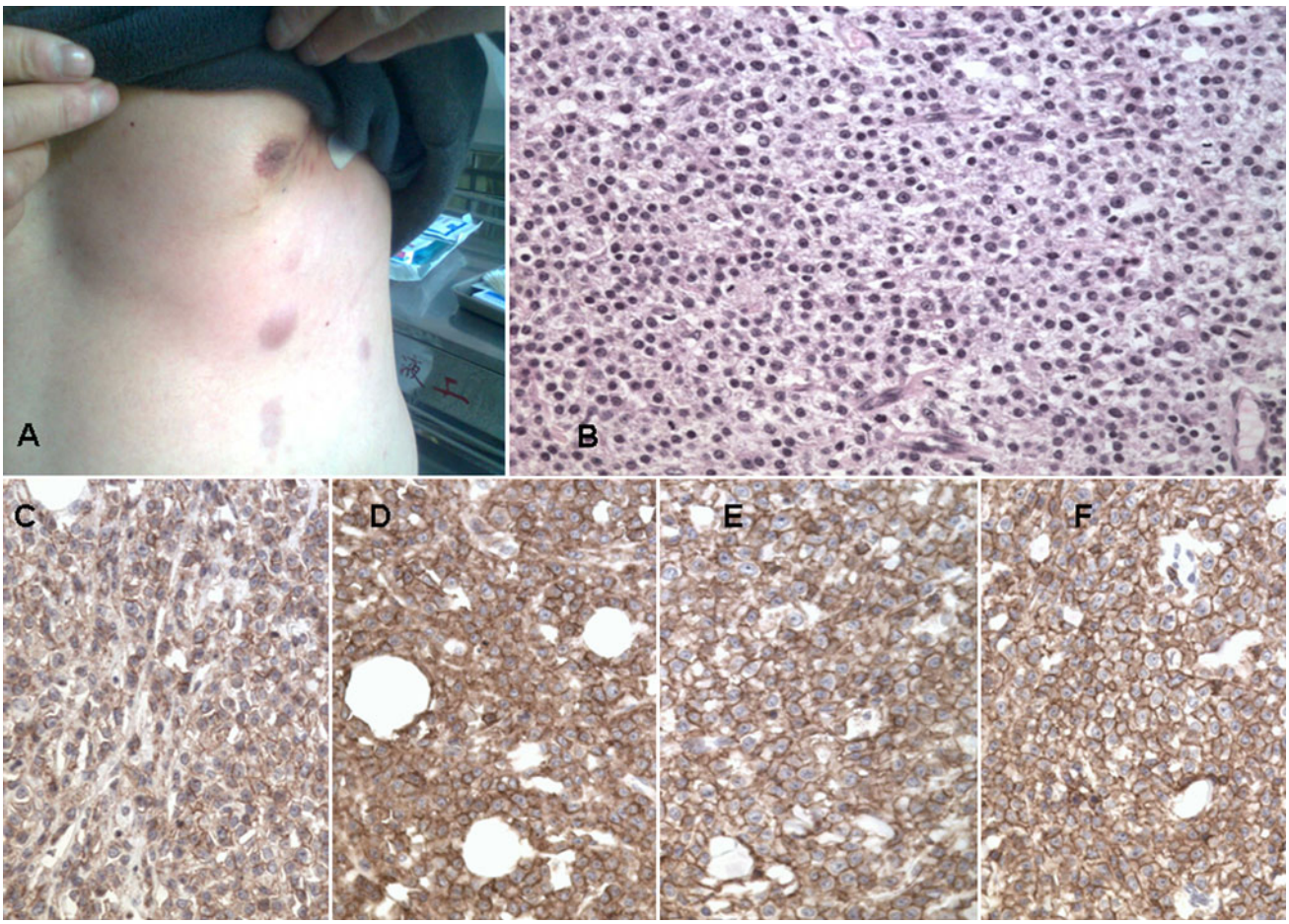

Fig. 2 Clinical picture and biopsy of skin lesions. **a** Erythematous nodules on the trunk. **b** Skin biopsy revealed lymphoid infiltration of the dermis, consisting of medium-sized monomorphic neoplastic cells (HE stain, ×200). **c–f** The neoplastic cells were immunohistochemically positive for CD4, CD56 (**c**), CD45 (**d**), CD43 (**e**), and CD123 (**f**), respectively, (×400). These findings are compatible with a diagnosis of BPDCN

streptococci, *Staphylococcus aureus* or *Enterococcus faecium* [4–7]. It is thought that induction of SR was attributed to cytokine release or cellular immune response during the course of infection. For example, cytokines including tumor necrosis factor-α, interleukin-2, and interferon-γ are known to increase in patient with severe infection, and these cytokines all showed antileukemic effect [10, 12]. And severe febrile infections stimulates the proliferation of natural killer (NK) cells and cytotoxic T lymphocytes, which were also relevant for SR [13]. Besides, the association of SR with preceding blood transfusions has been reported [2, 5, 6]. Blood components included cytotoxic antibodies against leukemic cells and allogeneic lymphocytes, which act similar to those described as graft-versus-leukemia (GVL) effect. However, nowadays, the packed red cells and platelet are devoid of leukocytes and are mostly irradiated. And most patients suffering from AML receive blood transfusions during therapy while SR has not been observed, so the theory has not been proven. In addition to infections and blood transfusion, the achievement of SR could be facilitated by G-CSF therapy, [14] which was also administered in our case. G-CSF as a single agent therapy has already achieved successful outcome in patients with hypoplastic AML or myelodysplastic syndrome (MDS). It has been shown that G-CSF can induce in vitro and in vivo differentiation of AML-M2 *t*(8; 21) and degradation of the AML1-ETO oncoprotein [15]. G-CSF could also suppress the leukemic cell clone by inducing apoptosis and suppressing the renewal of leukemic cells and induce the potential increase in effector cytotoxic cells [14]. We also reviewed some cases, in which neither infection nor blood transfusion or G-CSF therapy precede SR [3, 8], implying there might be other mechanisms of SR to be explored.

More interestingly, although long-term remission of AML was achieved, our patient suffered from secondary malignancy, named BPDCN. BPDCN, initially termed as blastic natural killer (NK)-cell lymphoma, agranular

Table 1 Review of the literature on cases of spontaneous remissions of AML-M5

Age/sex	Diagnosis	WBC (10^9/L)	BM blast (%)	CRP (mg/L)	LDH (U/L)	Karyotype	Infection	Transfusion	Remission dur. (months)	Outcome at last follow-up	Ref
42/M	M5a	0.5	91.5	43.10	336	Normal	Pneumonia	–	40+	Remission/2nd tumor	This case
41/F	M5	28	60	n.g.	n.g.	Normal	–	RBC	14	Relapse	[2]
74/F	M5	n.g.	90	n.g.	n.g.	*t*(9; 11) (q22; 23)	–	–	7	Relapse	[3]
61/M	M5a	0.9	90	n.g.	4,530	*t*(9; 11) (q22; 23)	Staph A/CNS	–	29+	Remission	[4]
28/M	M5b	1.3	26	n.g.	n.g.	Normal	Sepsis GGS	RBC/PLT	1	HSCT/relapse	[5]
64/M	M5b	44	40	n.g	1,620	Normal	Sepsis EF	RBC	14+	Remission	[6]
31/M	M5a with biphenotypic antigen	1.2	95	3,030	n.g.	Normal	Sepsis GGS	–	2	Relapse	[7]
47/F	M5	n.g.	n.g.	n.g.	n.g.	Trisomy 8	–	–	12	Relapse	[8]
83/F	M5b	43.6	60	n.g.	1,283	Trisomy 8	–	Leukoreduced irradiated RBC/PLT	0.5	Extramedullary Relapse	[9]
49/F	M5a	1.0	80	n.g.	n.g.	n.g.	–	n.g.	6	Relapse/death	[10]
47/M	M5b	7.4	80	n.g.	n.g.	Normal	Bacteremia *C. septicum*	–	4	Relapse/death	[11]

Staph A, *Staphylococcus aureus*; CNS, coagulase negative S*taphylococcus*; GGS Group G, *Streptococcus*; *C. septicum*, *Clostridium septicum*; EF, *Enterococcus faecium;* WBC, white blood cell; BM, bone marrow; CRP, C reactive protein; LDH lactate dehydrogenase; dur, duration; RBC, red blood cell; PLT, platelet; n.g., not given

CD4+ NK-cell lymphoma or agranular CD4+/CD56+ hematodermic neoplasm, is a rare, highly aggressive lymphoma and has been sporadically reported in Asian counties [16–18]. Recently, it is demonstrated that the original tumor cell derives from plasmacytoid dendritic cell (pDC) precursors, and the term of "blastic plasmacytoid dendritic cell neoplasm" evolves in the 2008 World Health Organization Classification system. The main clinical presentation of BPDCN is a solitary cutaneous lesion and subsequent involvement of the hematopoietic system, including bone marrow and lymph nodes. However, in some cases as well as our present case, the lesion is confined to the skin, which is considered to be associated with a more favorable prognosis [19–21].

As tumor cells of AML with cutaneous involvement often express the CD4 and CD56 antigen on their membranes, and our patient happens to have a history of AML with expression of CD56, and therefore, the main differential diagnosis is relapse of CD56+ AML with cutaneous involvement. The presence of myelomonocytic-specific markers, such as CD13, CD15, CD33, MPO, CD14, and CD64 should be helpful in making a diagnosis of CD56+ acute myeloid leukemia presenting in skin. In our case, the absence of MPO and CD33 on immunohistochemical analysis can distinguish from the myeloid leukemias, and the tumor cells strongly expressed CD123, which is a pDC-specific marker, can help to make a diagnosis of BPDCN.

The origin of BPDCN has been clarified to be derived from pDC precursors, which account for 0.1 % of peripheral blood mononuclear cells and accumulate in inflammatory sites to contribute to inflammatory and immune response. However, the lineage assignment of pDC to either a myeloid or a lymphoid derivation remains a matter of debate. Several lines of evidence favor a lymphoid origin, as most pDC cells express lymphoid-related antigens, such as CD2, CD5, CD7, granzyme B, Spi-B or TdT. These cells also express specific lymphoid-restricted transcripts for the invariant chain of the pre-T receptor, λ-like chain of IgV-preB and Spi-B. Data arguing for its myeloid origin is also accumulating. First evidence comes from the work by Olweus et al. [22], who demonstrated that CD123 high DC could be generated from a macrophage colony-stimulating factor (M-CSF)+ CD34+ progenitor. Besides, myeloid-associated marker CD13, CD33, and CD11c can be acquired by both normal and malignant pDC upon in vitro culture, [23] and up till now it has been reported that 10 patients with BPDCN express CD33, and one case expresses CD13 [24–26]. Actually, in the clinical setting,

up to 20 % of BPDCN are associated with or subsequently develop myeloid disorders [27]. In a series of 23 cases provided by Feuillard et al. [28], one patient suffered from chronic myeloid leukemia, another had MDS and 3 others demonstrated myelodysplastic features on the bone marrow Giemsa stain. Khoury et al. [27] also reported one case of AML and another case of MDS diagnosed during the follow-up of BPDCN. Likewise, our present case, which had a history of spontaneous remission of AML, is rare but more than just a coincidence. It could be explained by the hypothesis that malignant pDC cells and myeloid blast might have a common origin at the very early stage of differentiation.

As reported in the literature, this type of lymphoma is highly aggressive. Although early systemic chemotherapy may show a temporary effect in some rare patients, relapses occur soon afterward. Patients with recurrent BPDCN rarely respond to additional chemotherapy and ultimately convert to fulminant leukemia. Bekkenk et al. showed that age $\leq$40 years, presentation with a skin lesion only, high TdT expression, and aggressive treatment with acute leukemia protocol were associated with a more favorable prognosis [29]. Recently, a study involving 47 patients suggested that conventional chemotherapy and radiation therapy did not affect the course of the disease, while only allogeneic bone marrow transplanted could significantly prolong the overall survival regardless of the initial extension of the disease (BM-transplanted vs. non-BM-transplanted: 31.3 vs. 12.8 months) [30]. Thus, although our patient has shown a complete response to two cycles of chemotherapy, his ultimate prognosis is still grim. Allogeneic transplantation is recommended to achieve long-term remission.

In summary, we present an unusual case of spontaneous remission of AML followed by occurrence of BPDCN. Although the two diseases are distinct, they might have some inner connection, or they derive from a common myeloid progenitor. Discovery of such cases may shed further light on the pathobiology of BPDCN.

Acknowledgments The work was funded by National Natural Science Funds (81000193).

Conflict of interest There is no conflict of interest.

References

1. Fozza C, Bellizzi S, Bonfigli S, Campus PM, Dore F, Longinotti M. Cytogenetic and hematological spontaneous remission in a case of acute myelogenous leukemia. Eur J Haematol. 2004; 73(3):219–22. doi:10.1111/j.1600-0609.2004.00281.x.
2. Delmer A, Heron E, Marie JP, Zittoun R. Spontaneous remission in acute myeloid leukaemia. Br J Haematol. 1994;87(4):880–2.
3. Paul R, Remes K, Lakkala T, Pelliniemi TT. Spontaneous remission in acute myeloid leukaemia. Br J Haematol. 1994; 86(1):210–2.
4. Muller CI, Trepel M, Kunzmann R, Lais A, Engelhardt R, Lubbert M. Hematologic and molecular spontaneous remission following sepsis in acute monoblastic leukemia with translocation (9;11): a case report and review of the literature. Eur J Haematol. 2004;73(1):62–6.
5. Trof RJ, Beishuizen A, Wondergem MJ, Strack van Schijndel RJ. Spontaneous remission of acute myeloid leukaemia after recovery from sepsis. Neth J Med. 2007;65(7):259–62.
6. Mitterbauer M, Fritzer-Szekeres M, Mitterbauer G, Simonitsch I, Knobl P, Rintelen C, et al. Spontaneous remission of acute myeloid leukemia after infection and blood transfusion associated with hypergammaglobulinaemia. Ann Hematol. 1996;73(4): 189–93.
7. Maywald O, Buchheidt D, Bergmann J, Schoch C, Ludwig WD, Reiter A, et al. Spontaneous remission in adult acute myeloid leukemia in association with systemic bacterial infection-case report and review of the literature. Ann Hematol. 2004;83(3):189–94. doi:10.1007/s00277-003-0741-y.
8. Okagawa K, Kosaka M, Mima N, Goto T, Shinohara M, Tsuchihashi N, et al. Spontaneous complete remission in a patient with acute monocytic leukemia. Rinsho Ketsueki. 1990;31(11): 1872–7.
9. Daccache A, Kizhakekuttu T, Siebert J, Veeder M. Hematologic and cytogenetic spontaneous remission in acute monocytic leukemia (FAB M5b) with trisomy 8. J Clin Oncol. 2007; 25(3):344–6. doi:10.1200/JCO.2006.08.8500.
10. Musto P, D'Arena G, Melillo L, Cascavilla N, La Sala A, Ladogana S, et al. Spontaneous remission in acute myeloid leukaemia: a role for endogenous production of tumour necrosis factor and interleukin-2? Br J Haematol. 1994;87(4):879–80.
11. Al-Tawfiq JA, Al-Khatti AA. Spontaneous remission of acute monocytic leukemia after infection with *Clostridium septicum*. Int J Lab Hematol. 2007;29(5):386–9. doi:10.1111/j.1365-2257.2006.00846.x.
12. Jimemez C, Ribera JM, Abad E, Pintos G, Milla F, Junca J, et al. Increased serum tumour necrosis factor during transient remission in acute leukaemia. Lancet. 1993;341(8860):1600. doi:0140-6736(93)90739-4.
13. Kleef R, Jonas WB, Knogler W, Stenzinger W. Fever, cancer incidence and spontaneous remissions. Neuro Immuno Modulation. 2001;9(2):55–64. doi:10.1159/000049008.
14. Nimubona S, Grulois I, Bernard M, Drenou B, Godard M, Fauchet R, et al. Complete remission in hypoplastic acute myeloid leukemia induced by G-CSF without chemotherapy: report on three cases. Leukemia. 2002;16(9):1871–3. doi:10.1038/sj.leu.2402592.
15. Da Silva N, Meyer-Monard S, Menot ML, Parrado A, Lebel A, Balitrand N, et al. Functional G-CSF pathways in *t*(8;21) leukemic cells allow for differentiation induction and degradation of AML1-ETO. Hematol J. 2000;1(5):316–28. doi:10.1038/sj/thj/6200047.
16. Chen J, Zhou J, Qin D, Xu S, Yan X. Blastic plasmacytoid dendritic cell neoplasm. J Clin Oncol. 2011;29(2):e27–9. doi:10.1200/JCO.2010.30.5441.
17. Chang HJ, Lee MD, Yi HG, Lim JH, Lee MH, Shin JH, et al. A case of blastic plasmacytoid dendritic cell neoplasm initially mimicking cutaneous lupus erythematosus. Cancer Res Treat. 2010;42(4):239–43. doi:10.4143/crt.2010.42.4.239.
18. An G, Qi JY, Zou DH, Zhao YZ, Chen HS, Qiu LG. Blastic plasmacytoid dendritic cell neoplasm: two cases report and review of literatures. Zhonghua Nei Ke Za Zhi. 2009;48(3):189–92.
19. 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(1):55–9. doi:10.1016/j.prp.2010.05.008.
20. 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(7):1097–108. doi:10.1093/annonc/mdh268.
21. Rauh MJ, Rahman F, Good D, Silverman J, Brennan MK, Dimov N, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation, lacking cutaneous involvement: case series and literature review. Leuk Res. 2012;36(1):81–6. doi:10.1016/j.leukres.2011.07.033.
22. Olweus J, BitMansour A, Warnke R, Thompson PA, Carballido J, Picker LJ, et al. Dendritic cell ontogeny: a human dendritic cell lineage of myeloid origin. Proc Natl Acad Sci USA. 1997;94(23):12551–6.
23. Kohrgruber N, Halanek N, Groger M, Winter D, Rappersberger K, Schmitt-Egenolf M, et al. Survival, maturation, and function of CD11c− and CD11c+ peripheral blood dendritic cells are differentially regulated by cytokines. J Immunol. 1999;163(6):3250–9.
24. Garnache-Ottou F, Chaperot L, Biichle S, Ferrand C, Remy-Martin JP, Deconinck E, et al. Expression of the myeloid-associated marker CD33 is not an exclusive factor for leukemic plasmacytoid dendritic cells. Blood. 2005;105(3):1256–64. doi:10.1182/blood-2004-06-2416.
25. Giagounidis AA, Heinsch M, Haase S, Aul C. Early plasmacytoid dendritic cell leukemia/lymphoma coexpressing myeloid antigenes. Ann Hematol. 2004;83(11):716–21. doi:10.1007/s00277-004-0913-4.
26. Inoue D, Maruyama K, Aoki K, Nagano S, Maruoka H, Imai Y, et al. Blastic plasmacytoid dendritic cell neoplasm expressing the CD13 myeloid antigen. Acta Haematol. 2011;126(2):122–8. doi:10.1159/000328180.
27. Khoury JD, Medeiros LJ, Manning JT, Sulak LE, Bueso-Ramos C, Jones D. CD56(+) TdT(+) blastic natural killer cell tumor of the skin: a primitive systemic malignancy related to myelomonocytic leukemia. Cancer. 2002;94(9):2401–8. doi:10.1002/cncr.10489.
28. Feuillard J, Jacob MC, Valensi F, Maynadie M, Gressin R, Chaperot L, et al. Clinical and biologic features of CD4(+) CD56(+) malignancies. Blood. 2002;99(5):1556–63.
29. 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.
30. Dalle S, Beylot-Barry M, Bagot M, Lipsker D, Machet L, Joly P, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? Br J Dermatol. 2010;162(1):74–9. doi:10.1111/j.1365-2133.2009.09373.x.