Infantile CD4+/CD56+ hematodermic neoplasm

Haematologica 2007; 92:(9)e91-e93 DOI: 10.3324/haematol.11307

CD4+/CD56+ hematodermic neoplasm (formerly known as blastic natural killer (NK) cell lymphoma) is a rare and aggressive neoplasm with a poor prognosis. It is a recently described entity with a predilection for skin involvement.[1] Previously, the disease was thought to originate from NK cells because the tumor cells express the CD56 surface antigen. Recent evidence suggests a plasmacytoid dendritic cell origin for the tumor cells.[2,3] This lymphoma affects mainly elderly adults, and only a few pediatric cases have been reported.[4-7] We here describe, for the first time, a case of cutaneous CD4+/CD56+ hematodermic neoplasm presenting in an infant.

An 8-months-old male infant was brought to our Dermatology Outpatient Clinic with a two month history of a 2.5 cm×2.5 cm erythematous indurated plaque on his left upper back (Figure 1A), which was non-tender and firm on palpation. There were no palpable enlarged lymph nodes, and no hepatomegaly or splenomegaly. An incisional skin biopsy showed diffuse and dense infiltrate of medium-sized lymphoblastoid cells exhibiting irregularly-shaped nuclei in the dermis and subcutis (Figures 1B and C). The cytoplasm lacked azurophilic granules. There was a narrow Grenz zone separating the tumor cells from the epidermis, and epidermotropism of tumor cells was not seen. There were no neutrophils, eosinophils, or plasma cells. Angiocentricity, necrosis, or hemophagocytosis were not evident. The immunohistochemical stains (Figure 2) revealed positive reactions with CD4, CD45, CD56, CD123 and HLA-DR. Stains were negative with CD1a, CD3, CD20, CD30, CD34, CD117, myeloperoxidase (MPO), terminal deoxynucleotidyl transferase (TdT), and S-100 protein. Epstein-Barr virus RNA (EBER) was not detectable on the skin biopsy specimen by in situ hybridization. Monoclonal T cell receptor gene rearrangements were not demonstrated by polymerase chain reaction. A diagnosis of CD4+/CD56+ hematodermic neoplasm was made.

A complete blood count with differential count revealed neutropenia (6%) but no anemia or thrombocytopenia, and no blast cells were seen. Renal function, electrolytes, and liver function were normal. Imaging investigations including plain radiography of the chest and abdomen, abdominal ultrasound, radionuclide bone scan, and whole-body positron emission tomography/computed tomography (PET/CT) scan were all normal with no evidence of systemic disease. Lumbar puncture did not reveal any malignant cells in the cerebrospinal fluid. However, bone marrow biopsy showed marrow involvement by lymphoblastoid cells. The patient underwent systemic chemotherapy with cytarabine (for 7 days) and idarubicin (3 days), together with intrathecal methotrexate. The cutaneous mass over the left upper back regressed and almost completely disappeared. However, the patient suffered from neutropenia and sepsis after the first course of chemotherapy, and died 2 months after diagnosis.

CD4+/CD56+ hematodermic neoplasm is a rare aggressive lymphoma with poor prognosis. It primarily affects elderly adults, and the median age at diagnosis is 65 years.[5-7] Only a few pediatric cases have been described.[4] Although often limited to the skin initially, progression to more generalized disease (with bone marrow involvement and leukemia) eventually occurs in almost all patients.[6,7]

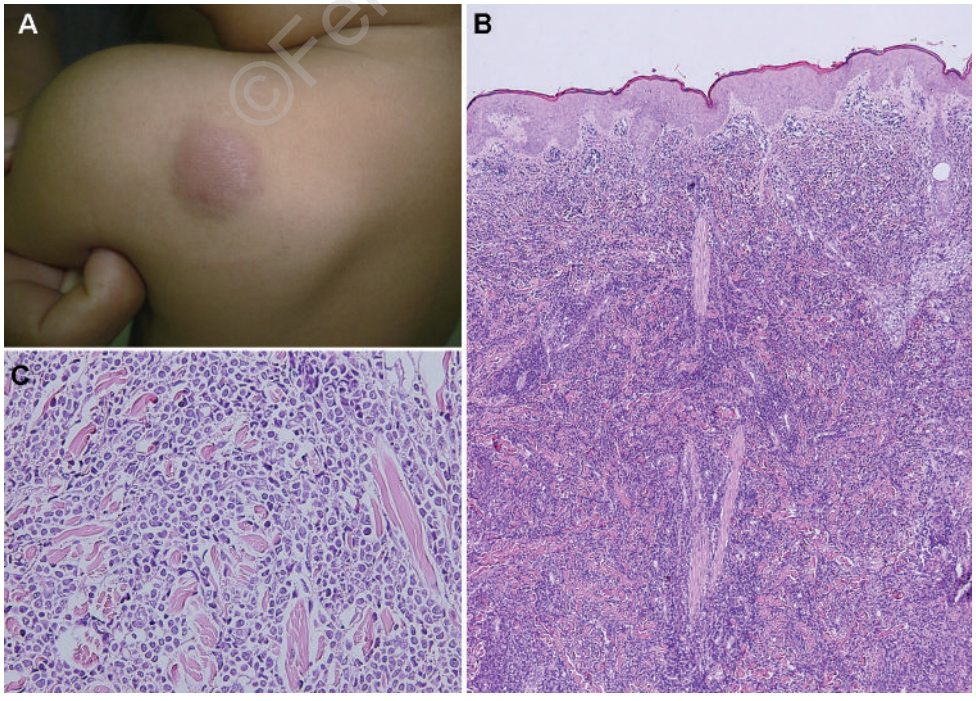

Figure 1. (A) Erythematous indurated plaque on the left upper back. (B) Skin biopsy showed diffuse and dense infiltrate in the dermis and subcutis (H&E: magnification 40X) (C) High-power view showing medium-sized lymphoblastoid cells (H&E: magnification 200X).

Associated lymphadenopathy, hepatosplenomegaly, and involvement of other organs including the central nervous system could sometimes be seen.[8] According to the recent World Health Organization-European Organization for Research and Treatment of Cancer classification, CD4+/CD56+ hematodermic neoplasms are immunohistochemically CD4+, CD56+, CD3-, and B-cell and myeloid antigen negative.[1]

Recently, the discovery of CD123 expression by tumor cells has shed light on the likely cell of origin for CD4+/CD56+ hematodermic neoplasms. Few normal cells are known to express the CD123 antigen, and the plasmacytoid dendritic cell is one of them.[2,3] CD4+/CD56+ hematodermic neoplasms and plasmacytoid dendritic cells also frequently share the expression of HLA-DR, BDCA-2, TCL-1 (T cell leukemia 1) and CLA (cutaneous lymphocyte-associated antigen).[9-11] In addition, CD4+/CD56+ hematodermic neoplasms have been found to express high levels of various plasmacytoid dendritic cell-related genes.[12] Since this entity is no longer regarded to be derived from natural killer cells, the term *blastic natural killer cell lymphoma* has been superseded by *CD4+/CD56+ hematodermic neoplasm*.

Whatever type or regimen of chemotherapy and radiotherapy is tried, the outcome remains dismal. Radiotherapy and/or chemotherapy with a variety of protocols generally produced a good initial response, but relapses occur in most cases in the following months. Presently, no therapies have demonstrated remissions for 5 years or more.[6] In a recent study conducted by Assaf *et al.* (2007) which included 20 patients with CD4+/CD56+ hematodermic neoplasm, the median survival was only 12 months.[7] Moreover, so far no standard therapeutic approach to this disease has been established. In our case, the patient appeared to have a good initial response to an acute myeloid leukemia protocol (cytarabine and idarubicin) with regression of the skin lesion, but unfortunately died of complications of chemotherapy.

In this report, we describe an 8-months-old infant with CD4+/CD56+ hematodermic neoplasm involving the skin and bone marrow. The clinical features, immature blastoid appearance, absence of azurophilic granules, lack of angiodestruction and necrosis, and EBV negativity differentiate it from EBV-positive nasal-type NK-cell lymphomas and aggressive NK-cell lymphoma/leukemia. The absence of markers for B-cells (CD20), T-cells (CD3), and myelomonocytic cells (myeloperoxidase, CD34, CD117) and the absence of monoclonal T cell receptor gene rearrangement excluded other types of lymphomas. The expressions of CD123 and HLA-DR support the derivation of tumor cells from plasmacytoid dendritic cells. This aggressive lymphoma affects mainly elderly adults, and to our knowledge, cutaneous presentation of this tumor at such a young age has never before been reported. This entity should therefore be considered in the differential diagnosis of malignant lymphomas in infants.

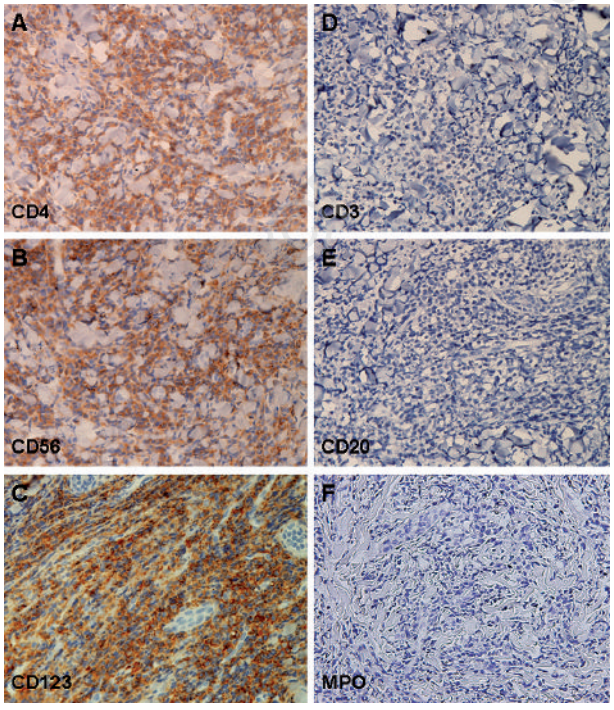

Figure 1. The immunohistochemical stains revealed positive reactions with CD4 (A), CD56 (B) and CD123 (C), and negative reactions with CD3 (D) CD20 (E), and MPO (F) (magnification 200X).

Stephen Chu-Sung Hu, MBBS, M.Phil[1], Kun-Bow Tsai, MD[2], Gwo-Shing Chen, MD, PhD [1,3], Po-Hung Chen, MD[1]

[1]Department of Dermatology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [2]Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [3]Department of Dermatology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

Key words: cutaneous lymphoma, hematodermic neoplasm, blastic natural killer cell

Correspondence: Po-Hung Chen, Department of Dermatology, Kaohsiung Medical University Hospital, No. 100, Shih-Chuan 1st Road, Kaohsiung, Taiwan. Tel: +886 7 3208214 Fax: +886 7 3216580. Email: m1238888@ms35.hinet.net

References

1. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105:3768-85.
2. Chaperot L, Bendriss N, Manches O, Gressin R, Maynadie M, Trimoreau F, et al. Identification of a leukemic counterpart of the plasmacytoid dendritic cells. Blood 2001; 97:3210-7.
3. Petrella T, Comeau MR, Maynadie M, Couillault G, De Muret A, Maliszewski CR, 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.
4. Ruggiero A, Maurizi P, Larocca LM, Arlotta A, Riccardi R. Childhood CD4+/CD56+ hematodermic neoplasm: case report and review of the literature. Haematologica 2006; 91:ECR48.
5. 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.

6. Petrella T, Bagot M, Willemze R, Beylot-Barry M, Vergier B, Delaunay M, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. Am J Clin Pathol 2005; 123:662-75.
7. Assaf C, Gellrich S, Whittaker S, Robson A, Cerroni L, Massone C, et al. CD56 lymphoproliferative disorders of the skin: A multicenter study of the Cutaneous Lymphoma Project Group of the European Organization for Research and Treatment of Cancer (EORTC). J Clin Pathol 2006; [Epub ahead of print]
8. 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.
9. Urosevic M, Conrad C, Kamarashev J, Asagoe K, Cozzio A, Burg G, et al. $CD4^{+}CD56^{+}$ hematodermic neoplasms bear a plasmacytoid dendritic cell phenotype. Hum Pathol 2005; 36:1020-4.
10. aye DL, Geigerman CM, Herling M, Eastburn K, Waller EK, Jones D. Expression of the plasmacytoid dendritic cell marker BDCA-2 supports a spectrum of maturation among $CD4^{+}$ $CD56^{+}$ hematodermic neoplasms. Mod Pathol 2006; 19:1555-62.
11. Petrella T, Meijer CJ, Dalac S, Willemze R, Maynadie M, Machet L, 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.
12. Dijkman R, van Doorn R, Szuhai K, Willemze R, Vermeer MH, Tensen CP. Gene-expression profiling and array-based CGH classify $CD4^{+}CD56^{+}$ hematodermic neoplasm and cutaneous myelomonocytic leukemia as distinct disease entities. Blood 2007; 109:1720-7.