Childhood CD4+/CD56+ hematodermic neoplasm: case report and review of the literature

Recently, rare CD4+/CD56+ hematodermic neoplasm has been described as a distinct clinicopathologic entity, with aggressive course and poor outcome. Skin is typically involved at presentation, but widespread dissemination to bone marrow is rapid. To date, no standardized therapeutic approach to this disease has been established. As its diffusion mainly concerns elderly patients, only a few paediatric cases have been documented. We report an additional case of CD4+/CD56+ hematodermic tumour that showed a good response to chemotherapy based on a lymphoma protocol. Moreover, we try to analyse features and outcome of a few other paediatric CD4+/CD56+ hematodermic tumours as they are reported in the literature.

Haematologica 2006; 91:(10)e132-e134

CD4+/CD56+ hematodermic neoplasms account for 0.7% of cutaneous lymphomas and are considered rare neoplasms with predominant skin involvement.[1] They have typical lymphoblastoid morphology and CD56 molecule expression, in the absence of commitment to the B, T-cell or myeloid lineage: expression of surface CD3 molecule is generally absent, as well as T-cell receptor (TCR) rearrangements and detectable Epstein-Barr virus genome (EBV).[2,3] Owing to their rarity, a clear nomenclature and characterization of malignancies arising from these cells has never been established in recent years.[4] Only in the recently published WHO-EORTC classification of cutaneous lymphomas[5] are they defined as *CD4+/CD56+ hematodermic neoplasms* and recognized as distinct clinicopathologic entities.[6] Although regarded as neoplasms related to natural killer (NK) cells for long time,[7,8,9] it is now accepted that CD4+/CD56+ hematodermic tumours derive from plasmocytoid dendritic cells (pDCs) as their leukaemic counterpart.[10,11,12] In this view, some authors have suggested that CD123, typically expressed on pDCs, can be used as specific cell markers to identify true pDC malignancies.[12] Notwithstanding, CD123 is not an exclusive marker for pDCs, as it is expressed in a variety of hematopoietic malignancies.[13] As far as controversies regarding pDCs themselves are concerned, recent laboratory findings suggest that mouse pDCs derive exclusively from estrogen-resistant myeloid progenitors,[14] but the question of their origin still needs to be definitively settled. CD4+/CD56+ hematodermic neoplasms mainly involve skin at diagnosis[15,16,17] with often indolent presentation, but manifest an aggressive and rapidly fatal course without delay. Systemic chemotherapy often results in a complete remission (CR), but quick relapses unresponsive to further treatment may be expected.[18] Only a few paediatric cases are reported in the literature, so little is known about their characteristics: although some authors propose moderately better prognosis for young age onsets,[13] poor outcome both in adults and in children is reported at present.[7,16]

Case Report

An eight-year-old boy presented a solitary red-brownish nodule (diameter 3×4 cm) on his left posterior thigh, followed after short time by multiple similar purpuric lesions all over the skin of the face, thorax and legs. Initial investigations for bleeding disorders were inconclusive, whereas the complete blood count revealed pancytopenia (Haemoglobin 8.8 g/dL, White Cell Count 2960/mm^3, Platelets 74×10^9/L). Circulating immature blood cells amounting to 30% were found. Hepatosplenomegaly was not reported. A left inguinal lymphadenopathy was evident and no interior organ involvement was observed. As malignancy was suspected, the child underwent inguinal lymph node (LN), skin and bone marrow (BM) biopsy, as well as BM aspirate.

Figure 1. Panels A-B: overview of the lymph node biopsy with a diffuse infiltrate composed of pleomorphic (small to medium-sized) blastic elements with scattered chromatin and frequent mitosis. (H&E: A original magnification 50x; B original magnification 250x). Panels C-D: details of the immunohistochemical pattern: blasts staining positive for CD4 (panel C) and CD56 and showing transcapsular pattern of growth involving the peri-lymph node fat tissue (panel D).(Avidin Biotin complex immunoperoxidase: C,D original magnification 100x).

Pathological examination of the LN biopsy revealed a lymphomatous infiltration composed of small to medium-sized elements without cytoplasmic azurophilic granules, effacing nodal architecture by diffuse proliferation (Figure 1). Blastoid cells stained negative for surface CD3, CD5, CD7, CD34, CD10, CD19, CD20, Granzyme B, CD13, CD14, CD33 and myeloperoxidase (MPO), and positive for CD56, CD4, CD2, CD45, HLA-DR, CD123 and TDT. An invasion of 90% blasts immunophenotypically similar to the LN profile was evident in the BM. Genomic investigation of tumour cells showed no TCR gene rearrangements and the EBER test was negative. All these findings were diagnostic of CD4+/CD56+ hematodermic neoplasm.[5] Its primary cutaneous and BM involvement was consistent with a IV-CNS negative Ann-Arbor stage. After diagnosis, the patient received treatment on the national AIEOP protocol for non-Hodgkin Lymphoma. Induction chemotherapy (CT) was administered with Vincristine (VCR), Daunomycin (DNM), Cyclophosphamide (CPM), high-dose Methotrexate (HD-MTX), Asparaginase (ASP) and Prednison (PDN), as well as intrathecal CT with MTX, Cytosine Arabinoside (ARA-C) and steroids (ITT). A consolidation course of therapy was performed with Etoposide (VP16), ARA-C, HD-MTX, 6-Mercaptopurine (6-MP) and ITT, followed by reinduction chemotherapy with Adriamycin (ADR), CPM, ARA-C, ASP, 6-Thioguanine (6-TG) and Dexamethasone (DEXA). Finally, the course I of maintenance consisted of 6-TG, PDN, ARA-C, ASP, CPM, VP16, MTX and VCR, followed by the second course with daily 6-MP and MTX once a week. Complete remission (CR) occurred after the first cycle and persisted throughout the treatment, until the second year from the beginning of the chemotherapeutic course was completed. At exactly two-years after diagnosis our patient was completely out of treatment. CR of

Table 1. Literature review of paediatric reports based on the expression of CD4. A: CD4+ group, defined as "CD4+/CD56+ hematodermic neoplasms" by WHO-EORTC.B: group of neoplasms CD4-.

Patient	Age/sex	Involvement	Skin primary site	Stage	EBV association	Immunophenotype*	Treatment CT	Treatment BMT/SCR	Outcome	Follow-up	Reference
A											
1	6mo/M	LN	-	I	-	$CD4^+/CD2^-/CD5^-/CD7^-$	x	-	DOD	10 mo	Chan *et al.*[8]
2	19/F	Skin	x	I	-	$CD4^+/CD20^-/CD79?^-$	x	-	ALIVE with disease	5 mo	Changet *al.*[7]
3	9/F	BM/LN	-	IV	-	$CD2^-/CD5^-/CD7^+/HLA\text{-}DR^+$	x	-	DOD	NA	Du Bois *et al.*[17]
4	18/M	Skin/BM/LN	x	IV	-	$CD4^+/CD2^-/CD5^-/CD7^+$	x	-	DOD	2 mo	Falcão *et al.*[16]
5	8/M	Skin/BM/LN/S	x	IV	-	$CD4^+/CD2^+/CD5^-/CD7^+$	x	-	ALIVE with CR	84 mo	Falcão *et al.*[16]
6	6/F	BM/LN/S	-	IV	-	$CD4^+/CD2^-/CD7^+/CD123^+$	x	x	ALIVE with CR	98 mo	Feuillard *et al.*[2]
7	8/M	Skin/BM/LN/L/S	x	IV	-	$CD4^+/CD2^+/CD7^-/CD123^+$	x	-	DOD	37 mo	Feuillard *et al.*[2]
8	14/M	Skin/BM	x	IV	-	$CD4^+/CD2^-/CD7^+/CD123^+$	x	-	ALIVE with CR	10 mo	Feuillard *et al.*[2]
9	18/M	Skin/BM/LN/S	x	IV	-	$CD4^+/CD43^+/TDT^+/CD2^-$	x	-	DOD	60 mo	Kim Y. *et al.*[18]
10	17/F	Skin	x	I	-	$CD4^+/TDT^-/CD20^-/CD68^+$	NA	NA	Lost to follow-up	NA	Kim Y. *et al.*[18]
11	12/M	BM/LN/L/S	-	IV	NA	$CD4^+/CD2^+/CD7^-/CD8^-$	-	-	DOD	2.5 mo	Wong *et al.*[8]
12	8/M	Skin/BM/LN	x	IV	-	$CD4^+/CD2^+/CD7^-/CD123^+$	x	-	ALIVE with CR	36 mo	present case
B											
1	15/F	Skin	x	I	-	$CD4^-/CD2^-/CD8^-/CD5^-/CD7^-$	x	-	ALIVE with CR	48 mo	Chan *et al.*[8]
3	14/F	BM/M/Pl/Per	-	IV	-	$CD4^-/CD2^+/CD5^+/CD7^+/CD34^+$	x	x	ALIVE with CR	39 mo	Hyakuna *et al.*[21]
4	14/M	BM/L/S	-	IV	NA	$CD4^-/CD2^+/CD7^-/HLA\text{-}DR^-$	-	NA	ALIVE with disease	NA	Ichikawa *et al.*[23]
5	13M	BM/LN/L/S	-	IV	-	$CD4^-/CD2^+$	NA	NA	DOD	NA	Imamura *et al.*[25]
6	14/F	Skin	x	I	-	$CD4^-/CD20^-/CD43^+$	x	-	ALIVE with disease	2 mo	Natkunam *et al.*[14]
7	18/M	BM/LN/L/S	-	IV	-	$CD4^-/CD7^-/CD2^+$	x	-	DOD	NA	Pirruccello *et al.*[22]
8	9/M	Skin/LN	x	II	-	$CD4^-/CD45^+/CD3^-/CD2^+/^-$	x	x	ALIVE with CR	15 mo	Shaw *et al.*[8]
9	15/M	BM/LN/M	-	IV	-	$CD4^-/CD2^+/CD5^+/CD7^+$	x	x	ALIVE with CR	NA	Yoshimasu *et al.*[24]

** all are surface CD3- and CD56+ malignancies without MPO, cytotoxic enzymes and TCR gene rearrangements. x = yes - = no*
LN: Lymph node; L: Liver; S: Spleen; BM: Bone Marrow; M: Mediastinum; Pl: Pleura; Per: Pericardium.
CR: Complete Response; NA: No Available information; DOD: Dead Of Disease; EBV: Epstein-Barr Virus; CT: Chemotherapy; BMT: Bone Marrow Transplantation; SCR: Stem Cell Reinfusion.

disease has so far persisted for 36 months.

Discussion

$CD4^+/CD56^+$ hematodermic malignancies are a rare entity of the hematolymphoid system, consisting of neoplasms with a high incidence of cutaneous involvement and risk of rapid leukaemic dissemination.[19] CD4 is usually positive, but no subclassification based on CD4 expression has ever been performed. Our comprehensive literature review focused on paediatric series is reported in Table 1 and shows paediatric cases variably treated with CT, bone marrow transplantation (BMT) and stem cell reinfusion (SCR). It was also attempted to analyse the impact of CD4 expression on the prognosis. Analysis of phenotypic and clinical features indicates the existence of two distinct groups inside this precursor neoplasm entity, suggesting two possible different subtypes, conceivably of different origin.[4,13] In particular, the literature reports a marked linkage between CD4 expression and primitive cutaneous involvement, whereas $CD4^-$ tumours seem mostly affect the mediastinum or other extranodal sites.[4] In our review, skin involvement accounted for 66% in the $CD4^+$ group, whereas it amounted only to 33% for the $CD4^-$ group. Mediastinal localization was reported in only one case in the $CD4^-$ group. Due to these close correlations between cutaneous involvement and CD4 expression, subclassification in terms of CD4 could be used. Although some authors have proposed an NK origin for the $CD4^-$ group of tumours, further clarification of this question is needed.[13] Based on the review of the literature and on the results of our analysis, CD4 expression does not appear to influence the prognosis: skin-restricted disease shows no better outcome than primarily disseminated disease,[20] so that both tumours should better be considered as primarily systemic neoplasms. Therefore, the response to treatment remains the most important prognostic factor. However, to date the treatment of paediatric $CD4^+/CD56^+$ neoplasms is not standardized and different therapeutic approaches are proposed for their treatment.[20] Several studies suggest that patients can best be treated with regimens designed for acute leukaemia.[22] Indeed CT alone seems to be inadequate to obtain long-term CR,[22,23] although some response to protocols for acute myeloid leukemia and lymphoid malignancies has been reported.[2,16] To date, allogeneic-BMT, as well as SCR[8], have been administered to patients with $CD4^+/CD56^+$ hematodermic neoplasms: Hyakuna *et al.*[21] performed BMT after achievement of CR with CT for acute lymphoid leukemia incorporating L-ASP, whereas one paediatric case has been successfully treated with umbilical cord blood transplantation by Yoshimasu *et al.*[24] Our additional case of $CD4^+/CD56^+$ hematodermic neoplasm shows an event free survival of 36 months so far following successful treatment based on a lymphoma protocol. Therefore, to date the exiguity of paediatric cases reported in the literature does not allow specific and definitive therapeutic conclusions to be drawn. Consequently, the optimal management of $CD4^+/CD56^+$ hematodermic neoplasm has not been exhaustively defined and the therapeutic role of more intensive treatment has to be clarified in large multi-institutional studies.

Antonio Ruggiero, MD, Palma Maurizi, MD, Luigi Maria Larocca, MD*
Annalisa Arlotta, MD, Riccardo Riccardi, MD

Division of Paediatric Oncology, Catholic University, Rome
**Institute of Anatomic Pathology, Catholic University, Rome*

Key words: children; CD4+/CD56+ hematodermic tumour; treatment.

Correspondence: Antonio Ruggiero, MD

Division of Paediatric Oncology Department of Paediatric Sciences

Catholic University Largo A. Gemelli 8 00168 Rome - Italy

Phone: ++39-06-3058203 Fax: ++39-06-3052751

E-mail: ruggiero@rm.unicatt.it

References

1. Petrella T, Bagot M, Willemze R, Beylot-Barry M, Vergier B, Delaunay M et al. Blastic NK-Cell Lymphomas (Agranular CD4+CD56+ Hematodermic Neoplasms). Am J Clin Pathol 2005;123:662-75.
2. Feuillard J, Jacob M-C, Valensi F, Maynadié M, Gressin R, Chaperot L et al. Clinical and biological features of CD4+ CD56+ malignancies. Blood 2002; 99(5):1556-63.
3. Matano S, Nakamura Sh, Nakamura S, Annen Y, Hattori N, Kobayashi K et al. Monomorphic Agranular Natural Killer Cell Lymphoma/Leukemia with No Epstein-Barr Virus Association. Acta Haematologica1999;101:206-8.
4. Karube K, Ohshima K, Tsuchiya T, Yamaguchi T, Suefuji H, Suzumiya J et al. Non-B, non-T neoplasms with lymphoblast morphology: further clarification and classification. Am J Surg Pathol. 2003 Oct;27(10):1366-74.
5. 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.
6. Petrella T, Dalac S, Maynadie M, Mugneret F, Thomine E, Courville P et al. The Group Francais d'Etude des Lymphomes Cutanes (GFELC). CD4+ CD56+ cutaneous neoplasms: A distinct haematological entity? Am J Surg Pathol 1999; 23(2): 137-46.
7. Chang SE, Choi HJ, Huh J, Choi JH, Sung KJ, Moon KC, Koh JK. A Case of Primary Cutaneous CD56+, TdT+, CD4+, Blastic NK-Cell Lymphoma in a 19-year-old Woman. Am J Dermatopathol 2002; 24(1):72-5.
8. Shaw PH, Cohn SL, Morgan ER, Kovarik P, Haut PR, Kletzel M, Murphy SB. Natural killer cell lymphoma. Report of two paediatric cases, therapeutic options, and review of the literature. Cancer 2001;91(4):642-6.
9. Jacob MC, Chaperot C, Mossuz P, Feuillard J, Valensi F, Leroux D et al.CD4+ CD56+ lineage negative malignancies: a new entity developed from malignant early plasmacytoid dendritic cells. Haematologica 2003;88: 941-55.
10. Chaperot L, Bendriss N, Manches O, Gressin R, Maynadié M, Trimoreau F et al. Identification of a leukaemic counterpart of the plasmacytoid dendritic cells. Blood 2001; 97(10):3210-17.
11. Trimoreau F, Donnard M, Turlure P, Gachard N, Bordessoule D, Feuillard J. The CD4+ CD56+ CD116- CD123+ CD45RA+ CD45RO- profile is specific of DC2 malignancies. Haematologica 2003; 88(03) ELT10.
12. Suzuki R, Nakamura S, Suzumiya J, Ichimura K, Ichikawa M, Ogata K et al. NK-cell Tumor Study Group. Blastic natural killer cell lymphoma/leukemia (CD56-positive blastic tumor): prognostication and categorization according to anatomic sites of involvement. Cancer 2005 ;104(5):1022-31.
13. Harman BC, Miller JP, Nikbakth N, Gerstein R, Allman D. Mouse plasmacytoid dendritic cells derive exclusively from estrogen-resistant myeloid progenitors. Blood 2006; 108(3):878-85.
14. Natkunam Y, Smoller BR, Zehnder JL, Dorfman RF, Warnke RA. Aggressive cutaneous NK and NK-like T-cell Lymphomas. Clinicopathologic, immunohistochemical and molecular analysis of 12 cases. Am J Surg Pathol 1999; 23(5):571-81
15. DiGiuseppe JA, Louie DC, Williams JE, Miller DT, Griffin CA, Mann RB, Borowitz MJ. Blastic natural killer cell leukemia/lymphoma: A clinicopathologic study. Am J Surg Pathol 1997, 21(10):1223-30.
16. Falcão RP, Garcia AB, Marques MG, Simões BP, Fonseca BA, Rodrigues ML, Foss NT. Bastic CD4 NK cell leukemia/lymphoma: a distinct clinical entity. Leuk Res 2002; 26(9):803-7.
17. DuBois SG, Etzell JE, Matthay KK, Robbins E, Banerjee A. Pediatric Acute Blastic Natural Killer Cell Leukemia. Leukemia & Lymphoma 2002; 43(4):901–6.
18. Kim Y, Kang MS, Kim CW, Sung R, Ko YH. CD4+CD56+ lineage negative hematopoietic neoplasm: so called blastic NK cell lymphoma. J Korean Med Sci. 2005 Apr;20(2):319-24.
19. Reimer P, Rudiger T, Kraemer D, Kunzmann V, Weissinger F, Zettl A et al. What is CD4+CD56+ malignancy and how should it be treated? Bone Marrow Transplant 2003; 32(7):637-46.
20. Herling M, Teitell MA, Shen RR, Medeiros LJ, Jones D. TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+ CD56+ blastic tumors of skin. Blood 2003; 101(12):5007-9.
21. Hyakuna N, Toguchi S, Higa T, Okudaira T, Taira N, Masuda M et al. Childhood blastic NK cell leukaemia successfully treated with L-asparagenase and allogeneic bone marrow transplantation. Pediatr Blood Cancer 2004; 42(7):631-34.
22. Pirruccello SJ, Bicak MS, Gordon BG, Gajl-Peczalska K, Gnarra DJ, Coccia PF. Acute lymphoblastic leukemia of NK-cell lineage: responses to IL-2. Leuk Res 1989; 13(9):735-43.
23. Ichikawa M, Kawai H, Komiyama A, Tsudo M, Miyasaka M, Kinoshita A, Nakazawa S. Functional p75 interleukin-2 receptor expression on the fresh blast cells in childhood acute lymphoblastic leukemia with natural killer cell properties. Am J Hematol 1991;36(4):259-64.
24. Yoshimasu T, Manabe A, Tanaka R, Mochizuki S, Ebihara Y, Ishikawa K et al. Successful treatment of relapsed blastic natural killer cell lymphoma with unrelated cord blood transplantation. Bone Marrow Transplant 2002 ;30(1):41-4.
25. Imamura N, Kusunoki Y, Kawa-Ha K Yumura K, Hara J, Oda K et al. Aggressive natural killer leukaemia/lymphoma: Report of four cases and review of the literature. Br J Haematol 1990;75:49-59.