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CORRESPONDENCE

A CD56-negative case of blastic natural killer-cell lymphoma (agranular CD4+/CD56+ haematodermic neoplasm)

SIR, Four cases of blastic natural killer (NK) cell-lymphoma were reported in a recent issue of this Journal.[1] This disease, also called agranular CD4+/CD56+ haematodermic neoplasm, represents a rare and distinct clinicopathological entity that was described recently.[2] The disease is characterized by its clinical presentation (high skin tropism, bone marrow involvement with or without leukaemia, very poor prognosis) and its molecular phenotype: CD4+, CD56+, CD123+ and 'lineage negative'. In an editorial in the same issue, an important role of CD56 antigen expression was highlighted in making the diagnosis of cutaneous lymphomas. The need for clinical and histopathological vigilance to recognize and establish the correct diagnosis was also emphasized.[3]

We report the surprising case of a blastic NK cell-lymphoma which does not express the CD56 antigen. An 87-year-old man presented with a 5-cm slightly reddish cutaneous nodule on the forehead (Fig. 1). The staging was normal and local radiotherapy was performed. A complete remission of 1 years's duration was obtained. The patient then relapsed with skin, cervical lymph node and bone marrow infiltration, and a leukaemic phase. Treatment with oral etoposide (Vepesid®; Bristol-Myers Squibb) induced a short stabilization. The patient died of his disease 2 years after the initial diagnosis.

Skin biopsy showed dermal infiltration by tumour cells which were predominantly medium sized. By immunohistochemistry on paraffin section these cells expressed only CD45, CD4 (Fig. 2a), CD43, HECA-452 and TCL1. CD43 was weakly expressed on the first biopsy but strongly expressed on relapse biopsies. CD68 was negative on the first biopsy but positive on relapse biopsies. On frozen sections, only CD2, CD4 and CD123 were positive. Markers of B-cell (CD20, CD79a), T-cell (CD3) myeloid-cell (CD13, CD14, CD15, CD33, CD117, MPO, lysozyme) and NK-cell (CD16, TIA-1, granzyme B) differentiation were negative. Importantly, CD56 was negative on both frozen and

LOW RESOLUTION FIG

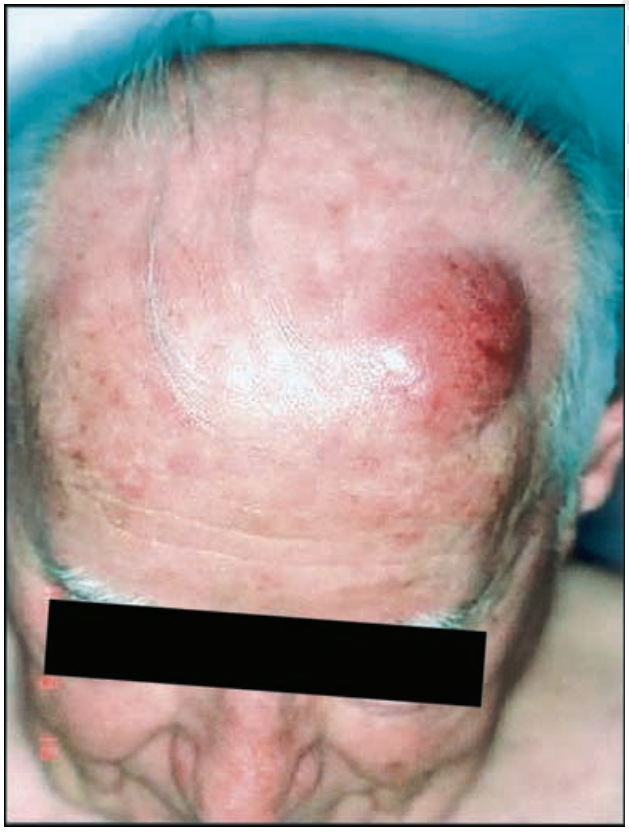

Figure 1. A reddish nodule is evident on the forehead.

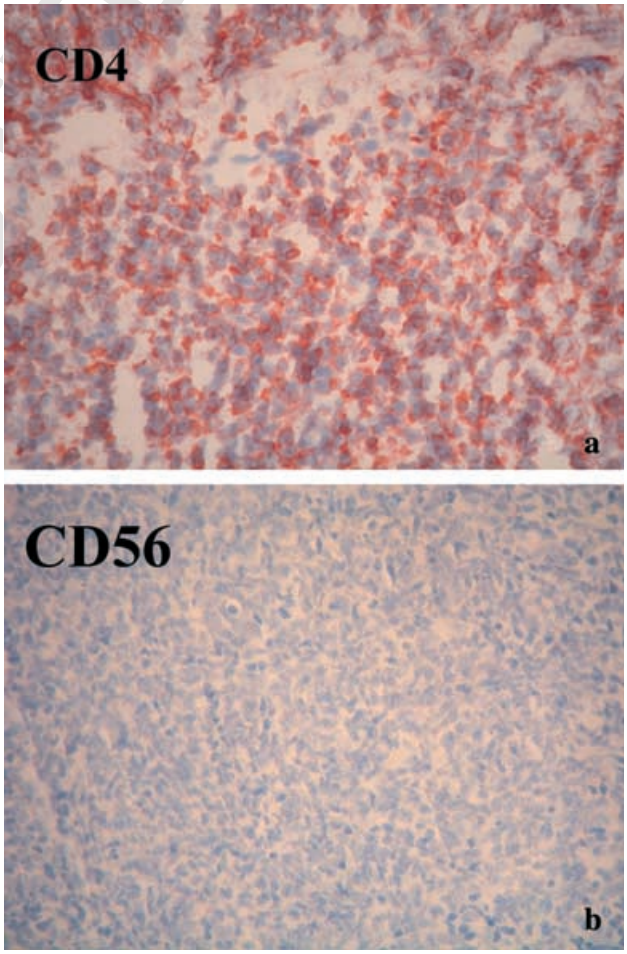

Figure 2. Immunostaining: (a) CD4 positive (paraffin section); (b) CD56 negative (paraffin section).

paraffin sections of the first biopsy and subsequent relapse biopsies (Fig. 2b).

This patient had the usual clinical presentation of blastic NK-cell lymphoma. The tumour cells showed a typical phenotype that was CD4+, CD43+, CD123+ and lineage negative. The case was so typical that initially we thought that the CD56 negativity was due to a technical problem and several additional controls were performed on paraffin and frozen sections.

As described in the new World Health Organization classification,[4] in which this tumour is listed as a blastic NK-cell lymphoma, the precise lineage of this neoplasm is unresolved and the proposal of a NK-cell origin was linked only to the expression of CD56 antigen. This link was tenuous at best due to the observation that several other nonlymphoid diseases express CD56, particularly tumours of myeloid origin. Several very recent studies have suggested an immature dendritic cell (IDC) origin for this entity.[5–7] IDCs are immune cells as originally identified. They display a peculiar phenotype: 'lineage negative' with expression of CD4, CD68 and high-level CD123; they are normally CD56 negative. A close relationship has been established between CD4+/CD56+ tumour cells and IDCs at the phenotypic[5,7,8] and functional levels.[6] The present case expresses CD123, HECA-452 and TCL1. These three antigens are known to be expressed by IDCs. CD123 (interleukin 3 α-chain receptor) is highly expressed on IDCs and at a lower level on blood dendritic cells.[9] It has been shown that CD123 is regularly expressed and is a hallmark of agranular CD4+/CD56+ haematodermic neoplasms.[5,7,8] It is not expressed by NK-cell lymphomas.[5] HECA-452 monoclonal antibody has also been demonstrated to be a good marker of IDCs.[10] TCL1 has been demonstrated to be expressed by both blastic NK-cell lymphomas and IDCs.[8]

The present case is the first reported case of a CD56-negative blastic NK-cell lymphoma (agranular CD4+/CD56+ haematodermic neoplasm). We think that this case is informative at two levels. First, it shows that the CD56 expression is not necessary to the histopathological diagnosis of the entity, and second, it reinforces the feeling that the disease probably originates from IDCs instead of NK cells. In this context the CD56 staining result must be interpreted carefully and with a great deal of objectivity.

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References

1 Child FJ, Mitchell TJ, Whittaker SJ *et al.* Blastic natural killer cell and extranodal natural killer cell-like T-cell lymphoma presenting in the skin: report of six cases from the U.K. *Br J Dermatol* 2003; **148**: 507–15.
2 Petrella T, Dalac S, Maynadie M *et al.* CD4+ CD56+ cutaneous neoplasms: a distinct hematological entity? Groupe Français d'Étude des Lymphomes Cutanés (GFELC). *Am J Surg Pathol* 1999; **23**: 137–46.
3 Slater DN. New CD56 positive and cytotoxic T-cell cutaneous lymphomas from the World Health Organisation. *Br J Dermatol* 2003; **148**: 385–7.
4 Chan JKC, Jaffe ES, Ralfkiaer E. Blastic NK-cell lymphoma. In: *The World Health Organisation Classification of Tumors: Tumors of Hematopoietic and Lymphoid Tissues* (Jaffe ES, Harris NL, Stein H, Vardiman JW, eds). Lyon: IARC Press, 2001; 214–5.
5 Petrella T, Comeau MR, Maynadie 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.
6 Chaperot L, Bendriss N, Manches O *et al.* Identification of a leukemic counterpart of the plasmacytoid dendritic cells. *Blood* 2001; **97**: 3210–7.
7 Feuillard J, Jacob MC, Valensi F *et al.* Clinical and biologic features of CD4(+)CD56(+) malignancies. *Blood* 2002; **99**: 1556–63.
8 Herling M, Teitell MA, Shen RR *et al.* TCL1 expression in plasmacytoid dendritic cells (DC2s) and the related CD4+CD56+ blastic tumors of skin. *Blood* 2003; **101**: 5007–9.
9 Maraskovsky E, Daro E, Roux E *et al. In vivo* generation of human dendritic cell subsets by Flt3 ligand. *Blood* 2000; **96**: 878–84.
10 Facchetti F, de Wolf-Peeters C, van den Oord JJ *et al.* Anti-high endothelial venule monoclonal antibody HECA-452 recognizes plasmacytoid T cells and delineates an 'extranodular' compartment in the reactive lymph node. *Immunol Lett* 1989; **20**: 277–81.

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