The CD4+ CD56+ CD116- CD123+ CD45RA+ CD45RO- profile is specific to DC2 malignancies

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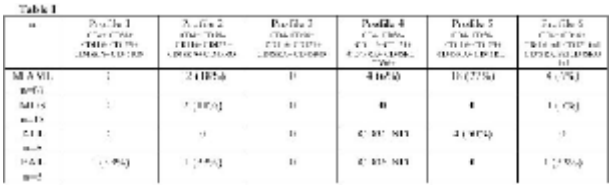
CD4+ CD56+ malignancies, also called *blastic NK lymphoma-leukemia,* are a recently described entity[1,2,3,4] and blast cells are considered as the leukemic counterpart of type 2 dendritic cells (DC2).[4] Differential diagnosis may sometimes be difficult because it is based mainly on the absence of B, T or myeloid lineage markers (lin-) in addition to CD4 and CD56 expression. This stresses the need for other specific criteria to recognize these tumors independently of the lin- profile. Like on normal DC2, co-expression of the IL-3 receptor (CD123) and CD45RA in the absence of GM-CSF receptor (CD116) and CD45RO was systematically observed in these tumors[2]. Moreover, CD36 was expressed in most cases. CD123 is widely expressed in AML.[5] It has been identified as a marker for AML stem cells (CD34+CD38- leukemia cells) [6]. CD116 has been preferentially associated with M4, M5 subtype of AML but is not specific[7]. Neither CD45RA nor CD45RO is lineage specific. CD36 is expressed by monocytic, erythroblast and megakaryoblast cells. This raises the question of the specificity of a DC2 immunophenotypic profile rather than of each individual marker. We therefore evaluated the expression of CD4, CD56, CD123, CD116, CD45RA, CD45RO and CD36 in acute leukemia and myelodysplastic syndromes (MDS) in order to evaluate the specificity of a *DC2 malignancies profile* that we defined as CD4+ CD56+ CD116- CD123+ CD45RA+ CD45RO-

Ninety-six patients were studied according to FAB and EGIL recommendations:[8,9] 67 with single lineage acute myeloid leukemia (AML) (M0: 13, M1: 13; M2: 20, M3: 4, M4: 9, M5: 4, M6: 2, M7: 1 unclassified), 8 with acute lymphoblastic leukemia (ALL), 3 with biphenotypic M+ B or M+T acute leukemia (BAL) and 18 with MDS. No CD4+CD56+ malignancy was diagnosed in this series of patients. Triple immunolabeling was performed on whole blood or purified bone marrow blast cells with FITC-conjugated CD116, PE-conjugated CD123, PECy5-conjugated CD45, and FITC-conjugated CD45RA, PE-conjugated CD45RO and FITC-conjugated CD36 monoclonal antibodies. Flow cytometry recognition of blast cells was based on their low levels of CD45 expression. A threshold of 30% was defined for considering blast cell positivity for a given marker. Six different immunophenotypic profiles were defined. Profile 1 was that of DC2 malignancies. Profiles 2 and 3 were equivalent to the profile of DC2 malignancies but with CD56 or CD4 being negative, respectively. Profile 4 was characterized by the expression of CD36 in the absence of CD4 and CD56 (CD4- CD56- CD123+ CD116- CD45RA+ CD45RO-). Profile 5 was CD4- CD56- CD123+ CD116- CD45RA+ CD45RO-, CD36 being indifferent. Finally, profile 6 was simply CD4+ CD56+, the other markers being indifferent. None of profiles 1, 2, 3 and 6 was found in ALL. Profile 5 (CD4- CD56-) was found in 50% of ALL. The complete DC2 malignancies profile (profile 1) was never observed in either AML or in MDS. This profile was observed only in one case of T+My+ BAL (Table I). Profile 2 (DC2 malignancies profile without CD56 expression) was not rare (18% of AML and 11% of MDS). Profile 3 (DC2 malignancies profile without CD4 expression) was never observed. Profile 4 (with CD36 and without both CD4 and CD56) was rare. The association CD123+ CD116- CD45RA+ CD45RO- with the negativity of both CD4 and CD56 (profile 5) was common in AML (27%) but absent in MDS. Profile 6 (co-expression of CD4 and CD56 only) was rare in both MDS and AML. Our results suggest that the complete DC2 malignancies profile is indeed specific to DC2 malignancies since it was never observed in our series of AML, ALL and MDS. By contrast, the loss of 1 or 2 of these criteria markedly diminished the specificity of this immunophenotypic profile. Therefore, the conjunction of our data with those of Feuillard *et al.*[2] strongly suggest that the complete DC2 malignancies profile can be used as a positive diagnosis criteria of CD4 CD56 malignancies. It is very interesting to note that this DC2 malignancies profile was found only in one case of a T+My+ biphenotypic acute leukemia. The question of its belonging to a bipotential T/DC2 cell precursor, as suggested in some reports of the literature,[10] is currently under investigation. In conclusion, we have shown that CD116, CD123, CD45RA and CD45RO markers are of interest in immunophenotyping acute leukemia together with CD4, CD56 and other lineage markers. They allow the definition of a CD4+ CD56+ CD116- CD123+ CD45RA+ CD45RO- DC2 malignancies profile independently of the lin- profile and would help to define border line cases.

Table 1. requency of the different immunophenotypic profiles in acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), acute lymphoblastic leukemia (ALL) and biphenotypic acute leukemia (BAL). ND : not done. Ind : indifferent



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