To the Editor:

When nasal lymphoma is present or a high percentage of granular lymphocytes is detected in the peripheral blood, a natural killer (NK) neoplasm is readily suspected. From the viewpoint of cell-surface antigen analysis, Emile et al. emphasized the importance of the phenotype, CD7+/CD5−/CD2+, as well as the expression of CD56 and the silence of T-cell receptor (TCR) for diagnosis of peripheral-stage NK neoplasm. The phenotype, CD7+/CD5−/CD2+, is particularly important in distinguishing NK lymphomas from the peripheral-stage lymphomas vaguely classified as non-B- or T-lineage lymphomas, in which the manifestation of peripheral-stage NK neoplasms such as granular lymphocytes, nasal lymphoma, and angiocentric histology is not overt. The absence of CD5 antigen as well as the expression of CD2 antigen seems to be prerequisite for the diagnosis of peripheral-stage NK neoplasms.

Thus, the phenotypic definitions for the diagnosis of peripheral-stage NK neoplasms appear to be more persuasive than before. On the other hand, the question remaining to be answered is how to distinguish more immature stages of NK neoplasms from cases of acute lymphoblastic leukemia (ALL)/lymphoblastic lymphoma (LBL). The differentiation pathways of T and NK lineages at immature stages are very close, and immature NK cells may well be free of mature function or functional molecules such as NK activity or the antigen detected with TIA-1 monoclonal antibody. Therefore, it may be very difficult to distinguish T- and NK-lineage neoplasms at the differentiation stages from which ALL/LBL arise. Such neoplasms are not clearly discussed in the Revised European-American Classification of Lymphoid Neoplasms, in which much consideration is made as to the derivation site of each neoplasm in the normal hematopoietic differentiation scheme.

In this respect, we also emphasize the phenotype of CD7+ CD5−/CD2+ CD56+ in ALL/LBL of NK lineage. In our laboratory, a total of 58 cases of T-lineage ALL/LBL have been phenotyped during the past 9 years. Nineteen of the 58 cases were CD3+ or CD1+ CD4−/CD8+ and of thymic stage. The rest were of early thymic (or prothymic) (CD3−/CD4−/CD8−) stage, including 10 cases of CD7+ CD5−/CD2+, 14 cases of CD7+ CD5+ CD2−, 4 cases of CD7+ CD5−/CD2−, and 11 cases of CD7+ CD5−/CD2−. The 11 cases of CD7+ CD5−/CD2+ included 7 cases with the expression of cytoplasmic CD3ε protein or CD3ε mRNA. Three of the 4 CD7+ CD5−/CD2− cases had the RO type expression of CD45 isoeformic antigen, in contrast to the RA type that CD7+ CD3−/CD4+ CD8− (early thymic or prothymic) ALL/LBL generally expressed. One of the 3 cases expressed CD56. This CD56+ case has already been published as LBL of probable NK lineage. In this case, the entire germline gene configuration of TCR (δ, γ, and β) or Ig, the presence of mRNA of CD3ε, the absence of CD3γ or CD3Δ6, and the detection of NK-specific dense granules with electron microscopy indicated the NK-lineage derivation. The neoplastic cells had no NK activity. Unexpectedly, the neoplastic cells expressed TdT mRNA as well as TdT protein, as detected by immunofluorescence. Recently, Ichinohazama et al. also reported a case of LBL of NK lineage with quite the same phenotype that expressed TdT. The expression of TdT is particularly notable, because the gene configuration of Ig or TCR was entirely of germline and, generally, because no information about the expression of TdT is available on physiological NK cells at this stage of differentiation. To our knowledge, these are the only case reports describing NK ALL/LBL.

The low incidence of the phenotype, CD7+ CD5−/CD2+ among the CD3−/CD4−/CD8− cases in our series can be regarded as reflecting the small number of NK cells compared with that of T-lineage cells, whereas the CD7+ CD5−/CD2− (CD3−/CD4−/CD8−) phenotype had formerly been classified into the immature stage of T-lineage cells without solid evidence in the early era of the phenotypic and genotypic analyses of leukemia/lymphoma. A few cases of CD7+ CD5−/CD2− blasts without monoclonal TCR gene rearrangement can be found in the reports. Still, the two phenotypes, CD7+ CD5−/CD2− and CD7+ CD5−/CD2−, were classified together as CD7+ CD5+/CD2− immature T-lineage cells in a recent proposal, and the CD7+ CD5−/CD2− phenotype were classified simply as an immature stage of T lineage in textbooks, although there have been no sufficient data on the comparative incidence of those two phenotypes. CD56 is not absolute for NK lineage, because the antigen was expressed in 2 thymic stage cases and a CD7+ CD5−/CD2− case in our results.

Any NK ALL/LBL cells found among the CD7− CD5−/CD2+ (CD56−) ALL/LBL cells should help to clarify the normal differentiation scheme of NK cells at immature stages.

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Acute Lymphoblastic Leukemia/Lymphoblastic Lymphoma of Natural Killer (NK) Lineage: Quest for Another NK-Lineage Neoplasm

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