**Differential Diagnosis of CD3\(^+\), CD56\(^-\) T-Cell Leukemias**

**To the Editor:**

Recently, Gentile et al\(^1\) reported what they believe to be a new disease, i.e., CD3\(^+\), CD56\(^-\) aggressive variant of large granular lymphocyte (LGL) leukemia. At presentation or during the course of the disease, all 3 patients were reported to have an absolute lymphocytosis, a moderate degree of thymocytopenia, and massive splenomegaly. Splenectomy specimens in all 3 cases showed preferential involvement of the splenic red pulp cords and sinuses. None of the lesions was positive for Epstein-Barr virus (EBV).

The differential diagnosis of T-cell lymphoproliferative disorders is complex and, indeed, some diseases may have been reported under more than one name. In their differential diagnosis, the investigators consider several lymphoproliferative disorders of T-cell and natural killer (NK)-cell derivation. However, they omit from their discussion many overlapping clinicopathologic and phenotypic features with the cases presented by Gentile et al.\(^1\) This disorder presents with marked hepatosplenomegaly, with only modest peripheral blood involvement. The patients are frequently anemic, leukopenic, and thymocytopenic. The malignant cells show preferential homing to the sinusoids of the splenic red pulp and liver. Prognosis is generally poor, with death reported in 4 of 6 cases in the literature and all 3 of the patients in our study for whom follow-up was available, despite aggressive chemotherapy.\(^2,4\)

Although γ/δ T cells are usually double negative for CD4 and CD8, expression of CD8 does occur in γ/δ T cells in peripheral lymphoid tissues,\(^6\) and a subset of γ/δ T-cell lymphomas are CD8\(^+\).\(^7,8\) Also significant is the expression of CD56 in all 3 of our cases in which it was studied and in 4 of 6 cases reported by Gaulard et al.\(^3,4\)

Thus, the phenotype of γ/δ T-cell lymphoma is very similar to that of the cases reported by Gentile et al.\(^1\): CD2\(^+\), CD3\(^-\), CD4\(^-\), CD5\(^-\), CD16\(^-\), CD25\(^-\), CD56\(^-\), CD57\(^-\), with variable expression of CD8. All cases were also negative for EBV sequences.\(^4\)

Additional studies would be required to evaluate the relationship of CD3\(^+\), CD56\(^-\) LGL leukemia to γ/δ T-cell lymphoma. Notably, the cases reported by Gentile et al.\(^1\) were studied only for CD3 and neither βF1 nor TCRβ were evaluated. γ/δ T-cell lymphomas are consistently βF1\(^-\) and TCRβ\(^-\); CD3 expression is seen in all instances. At the genotypic level, although all cases of γ/δ T-cell lymphoma have shown rearrangement of the T-cell receptor γ chain gene (TCRγ),\(^3,4\) β chain gene rearrangement (TCRβ) was seen in 2 of 5 cases studied.\(^4\) Thus, TCRβ rearrangement does not exclude the diagnosis.

S-100\(^+\), T-cell lymphoproliferative disease (S-100\(^+\), T-cell LPD) is another aggressive T-cell leukemia to be considered in the differential diagnosis. Marked splenomegaly has been reported in all cases.\(^7\) In contrast to hepatosplenic γ/δ T-cell lymphoma, and similar to CD3\(^+\) CD56\(^-\) LGL leukemia, most patients exhibit both lymphocytosis and lymphadenopathy. Despite aggressive chemotherapy, the prognosis is also poor, with death reported in all 7 cases reported with adequate follow-up.\(^3,7\)

Normally, S-100\(^+\) T cells are detected exclusively in a small percentage of peripheral blood lymphocytes belonging to the CD4\(^-\), CD8\(^+\) cell compartment.\(^8\) All 3 of the cases reported by Gentile et al.\(^1\) were CD8\(^-\), although in the literature only a proportion of cases of S-100\(^+\), T-cell LPD have been positive for CD8.\(^7\) In S-100\(^+\), T-cell LPD, the cells are EBV\(^-\) and express an αβ T-cell receptor. Also notable is the expression of several NK-cell–associated markers, including CD16 and CD56, but the absence of CD57. Thus, the phenotype of S-100\(^+\), T-cell LPD is also very similar to that of the cases reported by Gentile et al.\(^1\) Studies of S-100 protein would certainly be of interest.

The spectrum of diseases characterized as variants of T-cell chronic lymphocytic or prolymphocytic leukemia is broad, with many overlapping clinicopathologic and phenotypic features. As Gentile et al.\(^1\) note, CD56 expression is not specific and is found in many T-cell leukemias and lymphomas. We believe that further studies are required before one concludes that CD3\(^+\), CD56\(^-\) LGL leukemia is a newly described disease. We would advocate that all investigators pursue a multiparameter approach including cytogenetic analyses, if possible, to further delineate this group of T-cell malignancies.

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We appreciate the thoughtful comments of Kingma et al. We agree that the entities of S-100+, T-cell lymphoproliferative disorder (S-100+, T-cell LPD) and γδ T-cell lymphoma should be considered in the differential diagnosis of CD3+, CD56+ LGL leukemia. The clinicopathologic features, including the immunophenotype of the malignant cells, are very similar in S-100+, T-cell LPD and CD3+, CD56+ LGL leukemia. However, the S-100+ malignant cells lack the characteristic LGL morphology that is the hallmark of LGL leukemia. Although our cases of aggressive CD3+, CD56+ LGL leukemia were not studied for S-100 expression, typical cases of chronic LGL leukemia are S-100+. (Curtis A. Hanson, personal communication, November 1991). Therefore, we conclude that S-100+, T-cell LPD and CD3+, CD56+ LGL leukemia are distinct from each other.

The clinicopathologic presentation of γδ T-cell lymphoma is also very similar to that of CD3+, CD56+ LGL leukemia. However, patients with γδ T-cell lymphoma do not have the marked lymphocytosis typical for CD3+, CD56+ LGL leukemia. The infiltrating cells in the splenic red pulp cord in γδ T-cell lymphoma are described as being medium-sized lymphocytes with a regular or slightly indented nucleus and large pale cytoplasm. No specific comments were made as to whether these cells contained azurophilic granules typical of LGL. However, because the investigators considered T-LGL leukemia in the differential diagnosis of their cases, it would seem unlikely that these γδ T-cell lymphomas were LGL. Therefore, these cases of γδ T-cell lymphoma appear to be distinct from CD3+, CD56+ LGL leukemia. Nevertheless, patients with chronic T-LGL leukemia have been described in whom the leukemic LGL were γδ. These patients had features typical of the more usual αβ+ T-LGL leukemia. In view of these data and the comments of Kingma et al., expression of TCR αβ or γδ in CD3+, CD56+ leukemic T-LGL is of interest. We studied the peripheral blood mononuclear cells (PBMCs) of our 3 patients with flow cytometry analyses using TCR-1 (anti-αβ) and TCR-2 (anti-γδ) monoclonal antibody (Becton Dickinson, Mountain View, CA). PBMCs from patient no. 1 were TCR γδ+, whereas PBMCs from patients no. 2 and 3 were TCR αβ+. We conclude that, like chronic T-LGL leukemia, cases of aggressive CD3+, CD56+ LGL leukemia may be either αβ+ or γδ+. In the latter circumstances, there may be overlap between some cases of CD3+, CD56+ LGL leukemia and γδ T-cell lymphoma.

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