THE CONCEPT OF prolymphocytic leukemia (PLL) was introduced by Galton et al. in 1974 to describe what was interpreted as an uncommon variant of chronic lymphocytic leukemia (CLL) in which the predominant leukemic cell is characterized by large size, a moderate amount of cytoplasm with variable but usually moderate basophilia, relatively well condensed nuclear chromatin, and a large vesicular nucleolus. The disease was reported to occur predominantly in older males. In contrast to typical CLL, marked splenomegaly is common and peripheral lymphadenopathy is inconspicuous or absent in the majority of patients. There is usually a marked lymphocytosis; the mean absolute lymphocyte count in the initial series was \(335 \times 10^9/L\). The immunophenotype of the prolymphocytes in four of the 15 patients showed three cases to be of B-cell origin and one to be T cell.

Criteria for distinguishing B-PLL from typical or "classic" B-CLL were proposed by Melo et al in 1986. The term "prolymphocytic leukemia" was suggested for those cases with more than 55% prolymphocytes in the blood. In typical CLL, in contrast, the upper threshold for prolymphocytes is 10%. The term "chronic lymphocytic leukemia/prolymphocytic leukemia" (CLL/PL) was suggested for those cases with 11% to 55% prolymphocytes. The French-American-British (FAB) group subsequently proposed the term "mixed type" B-CLL for cases of CLL/PL and a second group in which there is a heterogeneous population of mature lymphocytes.

The first detailed description of the morphologic characteristics of T-PLL was published in 1986 by Matutes et al. In a series of 62 cases of PLL, 29 were of T-cell origin and 33 of B-cell origin. The described variation in the cytology of the predominant leukemic cell in some of the cases of T-PLL created some problem in regard to the morphologic unity of this disorder. Most troublesome was the recognition of a small cell variant in which the nucleolus was identified by electron microscopy. Additionally, the prolymphocytes in 12 of the 29 cases of T-PLL had irregular nuclear contours marked by folds and convolutions; in four of these 12 cases, minor populations of lymphocytes with polyploid or ceribriform nuclei resembling the lymphocytes in adult T-cell leukemia (ATCL) or Sezary syndrome were present. The morphologic heterogeneity of the prolymphocytes was paralleled by some degree of immunologic diversity. Although the leukemic lymphocytes in the majority of the cases were of T-helper/inducer phenotype, the lymphocytes in three cases had a suppressor phenotype and in three the lymphocytes had aberrant combined CD4, CD8 reactivity. The subsequent publication of the cytogenetic findings in 1987 in which an association of T-PLL with inv(14)(q11q32) and trisomy for 8q were reported added another important dimension to the studies of this entity and appeared to support the concept of T-PLL as a distinct subgroup of the postthymic lymphocyte proliferations.

Like some other postthymic T-cell proliferations such as granulated T lymphocytosis, T-PLL is a rare disorder. The 78 cases in the study by Matutes et al. in this issue of Blood is by any measure a very impressive number. The study is significant not only because of the large number of patients, but because it includes detailed clinical, immunologic, and cytogenetic data that invite a critical appraisal of the homogeneity of the process.

The morphologic variation in the leukemic cells in T-PLL described in 1986 and in the present study is a departure from the original concept of a prolymphocyte. Transmission electron microscopy should not be necessary to recognize a prominent nucleolus characteristic of the prolymphocyte that is the morphologically unifying feature of this disorder; this limitation may lead to incorrect classification of a substantial number of cases of this entity. Because of the rarity of the disorder and the prevailing impression of the morphology of a prolymphocyte, some if not many of the cases of the entity described by Matutes et al. have probably been misclassified as T-cell chronic lymphocytic leukemia (T-CLL) by other observers, including myself. This problem is acknowledged by the investigators who have assumed that some of the reported cases of T-CLL with similar chromosome abnormalities are probably T-PLL. The
small cell variant has the greatest potential for misclassification. The potential for misclassification will be highest for those cases of the small cell variant in which membrane surface markers are not performed.

The clinical features of some of the patients with T-PLL also contrast with the generally accepted features of PLL.\(^1\) Approximately half of the patients with T-PLL have lymphadenopathy; lower but significant numbers have hepatomegaly and skin lesions, which are a common finding in postthymic T-cell proliferations. Involvement of the central nervous system may also occur.

T-PLL is immunologically diverse, in contrast to some of the other postthymic proliferations such as Sezary syndrome, ATCL, and granulated T lymphocytosis, which are predominantly of either T-helper or T-suppressor immunophenotype. The immunologic findings in T-PLL parallel somewhat the findings in the node based peripheral T-cell lymphomas (PTCL), which are morphologically heterogeneous.\(^10-12\) The lymphocytes in the majority of cases of PTCL are of helper phenotype; a minority of cases is of suppressor or aberrant helper suppressor phenotype.

The cytogenetic demonstration of abnormalities of chromosome 14 involving bands q11 and q32 is an extremely important observation in T-PLL. However, although the leukemic cells in a high percentage of these cases manifest these abnormalities, the findings are not unique to this disorder and have been reported in other lymphoproliferative diseases including childhood T-lymphoblastic lymphoma, adult T-cell leukemia-lymphoma, B-cell precursor acute lymphoblastic leukemia (ALL) and a lymphoblastoid cell line.\(^14,17\) Earlier investigators have suggested that these abnormalities are common to T-cell proliferations.\(^14\) Notwithstanding, the high frequency of occurrence of these abnormalities in this group of patients suggests a relationship between these cases and, as the investigators propose, the combination of clinical and laboratory findings appear to identify T-PLL as a distinct clinical pathologic group of postthymic lymphoproliferative disorders.

Of additional interest in this study is the patient with ataxia telangiectasia. Earlier studies have shown a relationship between lymphocyte clones with the features of prolymphocytes and abnormalities involving chromosome 14 in specimens from patients with ataxia telangiectasia.\(^18,19\) In one such study of two sisters with ataxia telangiectasia, one of whom had a leukemia with features of prolymphocytes, a nonlymphocyte clone from the blood of the sister without leukemia showed the same 14q11 marker chromosome as the leukemic clone from the sister with leukemia. The lymphocytes in the blood of the sister with leukemia showed additional clonal abnormalities. As suggested by Matutes et al\(^18\) and others, the leukemic event in these patients may be triggered by the molecular event related to the additional chromosome abnormalities.

It will be important for other observers to carefully evaluate the morphology and cytogenetic data from patients with postthymic lymphoproliferative disorders with clinical and laboratory findings similar to those described in T-PLL. This particularly relates to those cases diagnosed as T-helper cell CLL or CLL with the aberrant CD4, CD8 phenotype. Presently, there is not an abundance of data on cytogenetic findings in the node-based PTCL. It is important that this group of postthymic T-cell processes be carefully studied to determine the presence and frequency of abnormalities involving chromosome 14 at bands q11 and q32.

Although T-PLL is a very rare disease, it is probably more common than apparent from the published cases. The failure to recognize it relates to the prevailing and not necessarily incorrect concept of the prolymphocyte. If diagnosticians continue to adhere to the concept of a prolymphocyte as it is quintessentially manifest in B-PLL, cases of T-PLL of the small cell variant and particularly those with markedly irregular nuclei will be misclassified. As noted in the earlier publication by Matutes et al on the morphology of T-PLL, minor populations of lymphocytes in four cases resembled Sezary cells or the lymphocytes in ATCL and in two of the cases in the present report, half of the lymphocytes had polylobated nuclei.\(^1\) In contrast to ATCL, the lymphocytes in T-PLL are CD7-positive and the patients are negative for human T-cell lymphotropic virus type I (HTLV-I) and do not have hypercalcemia. As noted, the majority of cases of T-PLL have probably been diagnosed as T-CLL or, in the absence of membrane markers, CLL or chronic lymphosarcoma cell leukemia. Based on morphology, these cases are generally viewed as low grade lymphoproliferative disorders and therapeutic decisions are based on that assumption. Because of the aggressive clinical course in the majority of patients, the inappropriate- ness of the diagnosis is quickly apparent. In addition, some cases in which the small cell variant is predominant at the outset, may show rapid evolution to a predominant population of cells in which nucleoli are prominent.

Notwithstanding the difficulties inherent in the use of the term prolymphocyte to describe the leukemic cells in all of the cases, the lymphoproliferative process described by Matutes et al appears to represent a distinct clinical pathologic subgroup of postthymic T-cell proliferation and these investigators are to be commended for bringing into more clear focus the clinical and laboratory features that in aggregate define this disease. The recognition of this entity emphasizes the importance of immunologic markers and cytogenetics in addition to morphology in the classification of hematopoietic proliferations. These studies are particularly relevant for this entity because of the less than clear relationship between morphology and cytogenetics in some of the cases.

More detailed studies of the morphology of T-PLL in bone marrow and lymph node biopsies and spleen specimens are necessary to determine the histopathologic relationship of this subgroup to the node based postthymic T-cell proliferations that, as noted, are also predominantly of helper phenotype and frequently marked by an aggressive clinical course. As a corollary of this, more cytogenetic studies are necessary on node-based T-cell proliferations to determine the prevalence of abnormalities involving bands q11 and q32 on chromosome 14.
REFERENCES


T-prolymphocytic leukemia [editorial]

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