T-Prolymphocytic leukemia: a rare clinical pathology

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Abstract

T-Prolymphocytic leukemia is a rare entity and represents 1% of all leukemias. This work describes its clinical and laboratory findings focusing on the differential diagnosis and treatment, and in particular, on the new purine analogs. Two paradigmatic cases are presented.

Key words: T-Prolymphocytic leukemia, purine analogs, pentostatin.

Introduction

Prolymphocytic leukemia (PLL) was first recognized as a clinical-morphological entity nearly twenty years ago. The first description was made in 1974, by Galton and colleagues[1], who published a series of fifteen patients previously considered as having a diagnosis of chronic lymphocytic leukemia. More recently, the use of cell markers in the study of lymphoid neoplasm enabled the identification of two prolymphocyte (PL) strains: B and T.[2] Their relative incidences are 80% and 20%, respectively.[3] Of all the leukemia types, PLL has an overall incidence of 4% to 6%, while its T variant constitutes only 1%.[3] This rarer variant has unique clinical laboratory characteristics and specific therapeutic indications, as well as a very limited prognosis.[4] We present two paradigmatic clinical cases that we had the opportunity to observe in the Intensive Care Unit for Hematological Patients (UTIDH) at the Hospital de Santa Maria.

Clinical Case 1

LCG, male, aged 65, admitted for asthenia, headache and purpuric skin lesions, with ten days of evolution. Physical examination revealed poor general condition, widespread petechia and ecchymoses, massive hepatosplenomegaly, generalized microadenopathies, and disseminated, violaceous, maculopapular skin lesions. The complementary tests revealed: Hb- 10.1 gr/dL, MCV-98,4fl, leukocytes-450,000/mm3 (neutrophils-6%, lymphocytes-3%, monocytes-2% and PL-89%); platelets – 75,000/mm3, AST-132 IU/I, ALT-146 IU/I, alkaline phosphatase-130 IU/I, lactate dehydrogenase-1887 IU/I, direct bilirubin 40 IU/I, total bilirubin-85 IU/I, and beta-2 microglobulin – 5.9 mg/dL. Myelogram revealed a bone marrow infiltration by 99% of cells with morphological characteristics of prolymphocytes, the immunophenotype of which was as follows: Tdt-2%; CD2-70%; CD3-0%; CD4-65%; CD8-0%; CD10-0%; CD19-0%; CD25-0%; HLA-DR-3%; FMC7-0%. Skin biopsy revealed dermal infiltration by lymphoid elements. Therapy was initiated with CHOP (cyclophosphamide – 750 mg/m2 i.v., d1; adriamycin 50 mg/m2 i.v., d1; vincristine -2 mg i.v., d1; prednisone – 100 mg p.o., d1-5), but the patient died twenty days after admission following a massive intracerebellar hemorrhage, as confirmed by necropsy.

Clinical Case 2

DCJ, male, aged 61, admitted with asthenia, weight loss and bleeding gums. Objective examination revealed poor general condition, pallor, fever, mucocutaneous hemorrhagic dyscrasia, moderate hepatosplenomegaly, generalized microadenopathies and generalized maculopapular skin lesions of the trunk and limbs. The complementary tests revealed: Hb 6.3 gr/dL; MCV -113.1 fl; leukocytes – 312,000/mm^3 (neutrophils-0%, lymphocytes-20%, PL-80%); platelets –10,000/mm^3; creatinine – 147 IU/I; and lactate dehydrogenase – 3,027 IU/I. Chest x-ray showed the presence of bilateral hilar adenopathies.

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Myelogram revealed infiltration by 90% of PL, acid phosphatase +, CD2+, CD3+, CD4+, CD7+, CD8-, CD19-, CD25-. Therapy was initiated with MINE (ifosfamide – 1.33gr/m²/d, iv, 3 days; mesna – 1.33gr/m2 iv, 4 hours after ifosfamide, followed by 500 mg, po, 4.8 and 16 hours after ifosfamide, 3 days; mitoxatrone – 8mg/m2, iv, 1 day; etoposide – 65mg/m2/d iv, 3 days). Myeogram performed 14 days after the therapy showed "partial remission" (infiltration by 5% of PL). On day 21, a cycle with similar characteristics was administered. Reassessment by myelogram, performed on day 20, showed infiltration by 6% of PL. On day 28, after the second treatment with MINE, therapy with 2-deoxycoformycin (4mg/m2, 12/12h, iv, 1 day) was begun. Reassessment by myelogram showed "complete remission" (low bone marrow cellularity, without atypical elements). The patient underwent both MINE cycles without complications, with a prolonged period of aplasia (25 days) after infusion of 2-deoxycoformycin. During this period, an interstitial pneumonia without isolation of pathogen, and spontaneous subarachnoid hemorrhage were diagnosed, from which the patient recovered with the therapy administered. The patient was discharged on day 83, with: Hb – 9.7gr/dL; leukocytes – 5,450/mm3 (neutrophils- 75%, lymphocytes- 22%, myelocytes 3%); and platelets -110,000/mm3. The peripheral blood lymphocyte counts were as follows: CD2-90% (270/mm3), CD19-4%(12/mm3), CD4-40%(120/mm3), and CD8-42%(126/mm3). The patient was in complete remission, as confirmed by myelogram.

Discussion

PLL occurs predominantly in male patients, and its onset usually occurs at fifty or sixty years of age.[4]

The symptoms are typically nonspecific, including weight loss, poor general condition, asthenia, anorexia, fever, and night sweats, with rapid deterioration.[4]

Objective examination usually reveals pallor and hepatosplenomegaly. In the case of the T variant, infiltrating skin lesions, generalized adenopathies and serous effusions are also observed.[4]

The main laboratory finding is hyperleukocytosis (leukocyte count above 100,000/mm3), which is more pronounced in the T variant (leukocyte count above 250,000/mm3), and must consist of more than 55% of PL.[4] The complementary tests that are essential for diagnosis, besides observation of the peripheral blood smears with PL identification and quantification, are: myelogram, which confirms bone marrow infiltration by PL, and leukocyte immune phenotyping. This is the technique that enables a differential diagnosis between B-PLL and T-PLL (see Table 1).

TABLE I

	T-PLL	B-PLL
Surface Ig	–	+
CD5	+	–
CD2	+	–
CD7	+	–
CD3	+	–
CD4	+/–	–
CD8	+/–	–
Tdt	–	–
HLADR	–	+
FMC7	–	+
CD10	–	+
CD19	–	+
CD20	–	+

T-PLL is characterized by a post-thymic phenotype (Tdt-, CD2+, CD5+, CD7+) in which PL are CD4+ and CD8- , in 65% of cases, 21% co-express both CD4+ and CD8+ phenotypes, and 13% are CD4- and CD8+.[4,5]

Karyotype reveals abnormalities on chromosome 14 in 76% of cases and trisomy 8 in 53% of cases.[5,6,7,8]

The serology for HTLV 1 is always negative.

The differential diagnosis is evident in B-PLL and other clonal proliferations of T-lymphocytes, with post-thymic phenotype: Sezary syndrome (SS), adult T-cell leukemia/lymphoma (ATCL) and T chronic lymphocytic leukemia (T-CLL).[4,8]

The prognosis is limited, with an average survival time of about six months,[5,9] therefore various therapeutic approaches have been attempted: polychemotherapy regimens with proven efficacy in lymphomas (e.g., CHOP, MINE),[8,9] splenectomy,[2] frequent leukapheresis[2], and Interferon-alpha:[2] always with limited therapeutic results. More recently, new purine analogs (fludarabine, pentostatin and cladribine) have been introduced in the therapeutic approach of chronic lymph proliferative diseases, which include PLL, with special emphasis on pentostatin in the

special case of T-PLL.[10,11,12] This drug, for which the therapeutic results published in the literature are controversial, is considered particularly effective in T-PLL CD4+ CD8- as it has specific cytotoxicity for the T-lymphocyte "helper" (CD4+, CD8-). Some authors have reported responses in more than 50% of patients [5,10,11,12]. However, this drug also has a high degree of toxicity, which includes, besides severe and prolonged immunosuppression (lasting up to one year) that is detrimental to lymphocytes CD4+ CD8-,[11,12] severe and common toxicity to the central nervous system.[11,12] Cladribine, a drug that has only recently become available, also shows promising results with low toxicity. Thus, new therapeutic prospects are emerging with the use of these drugs, either alone or in combination with other cytotoxic drugs, and these need to be confirmed through further investigations. It may be possible, in the near future, to increase the survival time of patients with T-PLL through the use of these therapeutic tools. ■

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