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# This Week's Citation Classic®

**Sen L & Borella L.** Clinical importance of lymphobiasts with T markers in childhood acute leukemia. N. *Engl. J. Med.* 292:828-32, 1975. [Labs. Virol, and Immunol., and Hematol. Sen.. St. Jude Children's Res. Hosp.. Memphis. TN]

**This paper describes a subtype of childhood acute lymphocytic leukemia (ALL), with a distinct clinical feature distribution. E-rosette positive ALL or T-ALL, which comprises 23 percent of the ALL studied, is associated with a higher proportion of older children, predominantly boys, a mediastinal eniargement (probably a thymic mass), and an elevated initial leukocyte count, al; features of poor prognosis in childhood ALL [The *SCI*® indicates that this paper has been cited in more than 435 publications.]**

## Clinical Features of T-ALL

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**In 1972, a few years after my medical school graduation in Argentina, I was awarded a Karnofsky Fellowship, giving me the opportunity to work abroad at St. Jude Children's Research Hospital, Memphis, Tennessee, in the Laboratories of Virology and Immunology, under the supervision of Luis Borella. At that time, one of Borella's concerns was to find an explanation for the unusually poor prognosis of a subset of children with acute lymphocytic leukemia (ALL). The children in this subset had similar cytomorphology and were able to respond to combination chemotherapy, but only half remained in long-lasting, continuous, complete remission. The hypothesis was that ALL could have different lymphoid cell lineages. With the tools then available to characterize lymphoid cells in ALL samples at diagnosis, we tried to identify B cells by the presence of surface immunoglobulins and T cells by E-rosette formation with sheep erythrocytes.**

**We did not have long to wait for the differentiating results. The fourth bone marrow ALL sample studied presented blast cells forming beautiful spontaneous E-rosettes,[1] suggesting for the first time that the clinical outcome might be related to the origin of the leukemic cells, that is, T-ALL. We immediately communicated our results to the hospital staff. I still remember my excitement when the director of the hospital, Donald Pinkel, asked us if we were ready for an official communication. Although we had no doubt about our results, I was concerned that this observation might just be an ALL artifact. The uncertainty lasted until the second T-ALL appeared and thereafter we defined two groups of ALL, E-rosette positive and E-rosette negative. After studying 48 consecutive ALL samples, all negative for surface immunoglobulins, we established that children with E-rosette positive blasts or T-cell leukemia had distinct clinical characteristics and poor outcomes. A few months later, G. Flandrin and coworkers[2] reported the existence of a few cases of B-cell ALL with very poor prognoses in which tumor cells resembled the tumor cells of Burkitt's lymphoma patients. Our further studies of childhood T-ALL blasts suggested that they mimicked thymic cells more than mature T cells.[3,4] This assumption was confirmed five years later by Immunophenotyping with monoclonal antibodies.[5] Since then, hundreds of publications have emerged and the immunophenotyping of ALL with monoclonal antibodies is currently a routine test used to define distinct clinical entities and prognostic factors for better management of leukemia therapy.**

**This was a marvelous experience for me. In 1979, back in Argentina, I received the Pablo San Martin Award sponsored by FUNDALEU ( a national leukemia foundation) for my contribution to ALL research.**

**Our work has provided a tool to increase our knowledge in T-cell ontogeny and in clinical hematology. To quote Michael J. Borowitz, our initial ALL hypothesis "is still valid today, in that it expresses the philosophy by which investigators approach analysis of prognostic factors."[6] (p. 761)**

**I would like to dedicate this commentary to the memory of my best teacher and good friend, Luis Borella, who shared with me all the joys of research during my four years in the US.**

! **Borella L** & **Sen L.** T cell surface markers on lymphobiasts from acute Iymphocync leukemia. *J Immunol.* 111: 1257-60. 1973, (Cited 165 times.) *2.* **Flandrin G. Brouet J C, Daniel M T & Preud'homme J L.** Acute leukemia with Burkitt's tumor cells: a study of six cases with special reference to lymphocyte markers. *Blood* 45:183-8. 1975. (Cited 225 times.) 3 **Borella L** & **Sen** L. h receptors on blasts from untreated acute lymphocync leukemia (ALL): comparison of temperature dependence of E rosettes formed by normal and leukemic lymphoid cells. *J. Immunol* 114:187-90. !975. (Cited 145 times.) 4. **Sen L, Mills B & Borella L.** Erythrocyie receptors and thymus-associated antigens on human thymocytes, mitogen-induced blasts, and acute leukemia blasts. *Cancer Res.* 38:2436-41. 1976. 5 **Reinherz E L, Kung P C, Goldstein** G. **Levey R H** *&* **Schlossman** S **F.** Discrete stages of human intraihymic differentiation: analysis of normal thymocytes and leukemic lymphoblasls of T lineage. *Proc. Nai. Acad, Sci. USA* 77:1 588-92. 1980. (Cued 1.670 times.)

6. **Borowitz MJ.** Immunologic markers in childhood acute lymphoblastic leukemia. *Hemaiol. Oncol. Clin. N. Amer.* 4:743-65, 1990.

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