condensed chromatin. In many cases the nuclear membrane is deeply subdivided, imparting a convoluted appearance. In keeping with the aggressive clinical behavior, the mitotic rate is high. As with other rapidly growing lymphoid tumors, interspersed macrophages ingesting apoptotic tumor cells may impart a "starry sky" appearance (shown in Fig. 13-15).

Because of their different responses to chemotherapy, ALL must be distinguished from acute myeloid leukemia (AML), a neoplasm of immature myeloid cells that can cause identical signs and symptoms. **Compared with myeloblasts, lymphoblasts have more condensed chromatin, less conspicuous nucleoli, and smaller amounts of cytoplasm that usually lacks granules.** However, these morphologic distinctions are not absolute and definitive diagnosis relies on stains performed with antibodies specific for B- and T-cell antigens (Fig. 13-6*B* and *C*). Histochemical stains are also helpful, in that (in contrast to myeloblasts) lymphoblasts are myeloperoxidase-negative and often contain periodic acid-Schiff–positive cytoplasmic material.

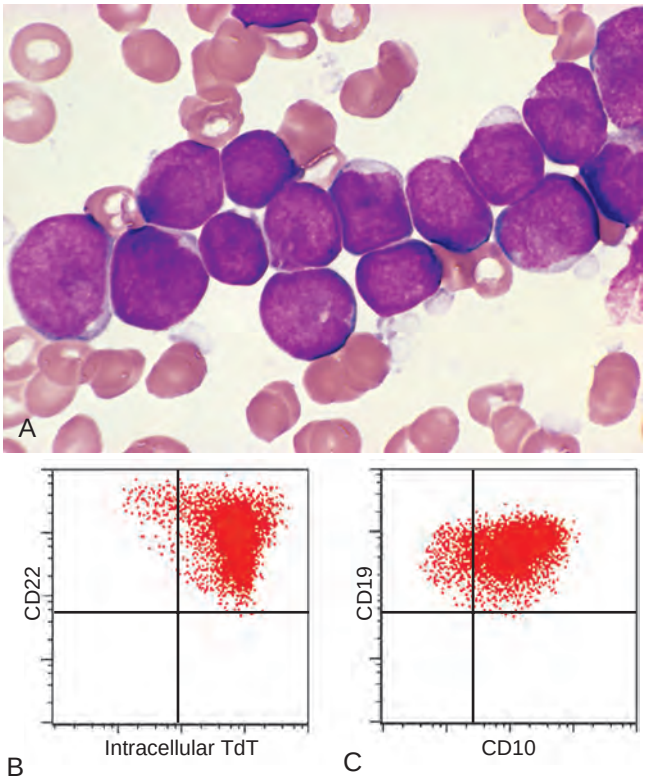

Figure 13-6 **A,** Acute lymphoblastic leukemia/lymphoma. Lymphoblasts with condensed nuclear chromatin, small nucleoli, and scant agranular cytoplasm. **B** and **C** represent the phenotype of the ALL shown in **A,** analyzed by flow cytometry. **B,** Note that the lymphoblasts represented by the red dots express terminal deoxynucleotidyl-transferase (TdT) and the B-cell marker CD22. **C,** The same cells are positive for two other markers, CD10 and CD19, commonly expressed on pre-B lymphoblasts. Thus, this is a B-ALL. (**A,** Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas; **B** and **C,** courtesy Dr. Louis Picker, Oregon Health Science Center, Portland, Ore.)

Immunophenotype. Immunostaining for terminal deoxynucleotidyl transferase (TdT), a specialized DNA polymerase that is expressed only in pre-B and pre-T lymphoblasts, is positive in more than 95% of cases (Fig. 13-6*B*). B- and T-ALLs are distinguished with stains for B- and T-cell–specific markers (summarized later).

B-ALLs are arrested at various stages of pre–B-cell development. The lymphoblasts usually express the pan B-cell marker CD19 and the transcription factor PAX5, as well as CD10. In very immature B-ALLs, CD10 is negative. Alternatively, more mature "late pre-B" ALLs express CD10, CD19, CD20, and cytoplasmic IgM heavy chain (μ chain).

Similarly, T-ALLs are arrested at various stages of pre–T-cell development. In most cases the cells are positive for CD1, CD2, CD5, and CD7. The more immature tumors are usually negative for surface CD3, CD4, and CD8, whereas "late" pre–T-cell tumors are positive for these markers.

Clinical Features. Although ALL and AML are genetically and immunophenotypically distinct, they are clinically very similar. In both, the accumulation of neoplastic "blasts" in the bone marrow suppresses normal hematopoiesis by physical crowding, competition for growth factors, and other poorly understood mechanisms. The common features and those more characteristic of ALL are the following:

- *Abrupt stormy onset* within days to a few weeks of the first symptoms
- *Symptoms related to depression of marrow function*, including fatigue due to anemia; fever, reflecting infections secondary to neutropenia; and bleeding due to thrombocytopenia
- *Mass effects caused by neoplastic infiltration* (which are more common in ALL), including bone pain resulting from marrow expansion and infiltration of the subperiosteum; generalized lymphadenopathy, splenomegaly, and hepatomegaly; testicular enlargement; and in T-ALL, complications related to compression of large vessels and airways in the mediastinum
- *Central nervous system manifestations* such as headache, vomiting, and nerve palsies resulting from meningeal spread, all of which are also more common in ALL

Prognosis. Pediatric ALL is one of the great success stories of oncology. With aggressive chemotherapy about 95% of children with ALL obtain a complete remission, and 75% to 85% are cured. Despite these achievements, however, ALL remains the leading cause of cancer deaths in children, and only 35% to 40% of adults are cured. Several factors are associated with a worse prognosis: (1) age younger than 2 years, largely because of the strong association of infantile ALL with translocations involving the *MLL* gene; (2) presentation in adolescence or adulthood; and (3) peripheral blood blast counts greater than 100,000, which probably reflects a high tumor burden. Favorable prognostic markers include (1) age between 2 and 10 years, (2) a low white cell count, (3) hyperdiploidy, (4) trisomy of chromosomes 4, 7, and 10, and (5) the presence of a t(12;21). Notably, the molecular detection of residual disease after therapy is predictive of a worse outcome in both B- and T-ALL and is being used to guide new clinical trials.