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# Advances in the molecular pathobiology of B-lymphoblastic leukemia

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**Summary** B-lymphoblastic leukemia/lymphoma, also known as B-acute lymphoblastic leukemia, is derived from B-cell progenitors. B-acute lymphoblastic leukemia occurs predominantly in children, but can occur at any age. Risk-adapted intensive chemotherapy is effective in treating most children with B-acute lymphoblastic leukemia, but this approach is less successful in adults. Recent developments in genome-wide genetic analysis in B-acute lymphoblastic leukemia have provided insights into disease pathogenesis and prognosis. B-acute lymphoblastic leukemia cases usually carry a primary genetic event, often a chromosome translocation, and a constellation of secondary genetic alterations that are acquired and selected dynamically in a nonlinear fashion. These genetic changes commonly affect cellular mechanisms that control B-cell differentiation and proliferation. The cooperative interaction between inactivation of hematopoietic transcription factors involved in differentiation (class II mutation) and activating mutations involved in cell proliferation (class I mutation) is reminiscent of the pathogenic model of acute myeloid leukemia. The resulting improved molecular understanding of B-acute lymphoblastic leukemia is helping to refine disease risk stratification and discover new therapeutic approaches for patients with refractory disease. In this review, we first summarize the clinicopathologic and immunophenotypic features of B-acute lymphoblastic leukemia and introduce current understanding of B-cell development and B-acute lymphoblastic leukemia leukemogenesis. We then focus on recent advances in genetic analysis and gene expression profiling of B-acute lymphoblastic leukemia and discuss the implications of these findings for disease evolution, risk prediction, and possible novel therapeutic approaches.


## 1. Introduction

B-cell lymphoblastic leukemia/lymphoma, also known as precursor (pre) B-cell or simply acute lymphoblastic leukemia (B-ALL), is a malignant neoplasm derived from B-cell progenitors. B-ALL is predominantly a childhood disease but can occur at any age. Outcome for pediatric patients with B-ALL treated appropriately has dramatically improved over the last 2 decades; 5-year overall survival is greater than 80%. In adults with B-ALL, conventional chemotherapy has been less successful, with a disease-related mortality of approximately 60%. Improvements in outcome are mostly attributable to risk-adapted intensive chemotherapy. It is well recognized that overall prognosis and risk of relapse in patients with B-ALL correlate with genetic alterations. Current risk-stratification schemes are mostly based on the presence and type of recurrent

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cytogenetic abnormalities. Refractory disease, however, is not exclusively associated with any particular cytogenetic abnormality; poor outcome occurs in a subset of patients in all at-risk groups. A major clinical challenge is to improve the risk-stratification algorithms and discover new therapeutic approaches for patients with refractory disease. Genome-wide genetic analyses of B-ALL cases have provided insights into disease pathogenesis and response to therapy. In this review, we summarize the general clinicopathologic, immunophenotypic, and cytogenetic features of B-ALL. We then focus on recent advances in our understanding of B-ALL at the molecular level and the implications of these findings for disease classification, prediction of prognosis, and possible impact on future therapies.

## 2. Clinical presentations

Approximately 75% of patients with B-ALL are younger than 6 years, and 80% to 85% of cases arise during childhood. The clinical presentation is variable, and symptoms can appear insidiously or acutely, depending on the extent of disease. Fever, fatigue, bone pain, arthralgia, headache, vomiting, and alteration of mental status can be observed [1]. Rarely, patients are asymptomatic, and B-ALL is diagnosed initially by routine peripheral blood smear examination. Lymphadenopathy, hepatosplenomegaly, and other extramedullary sites of disease are common, with a predilection for the central nervous system and testes, so-called sanctuary sites (Fig. 1). B-ALL also can present

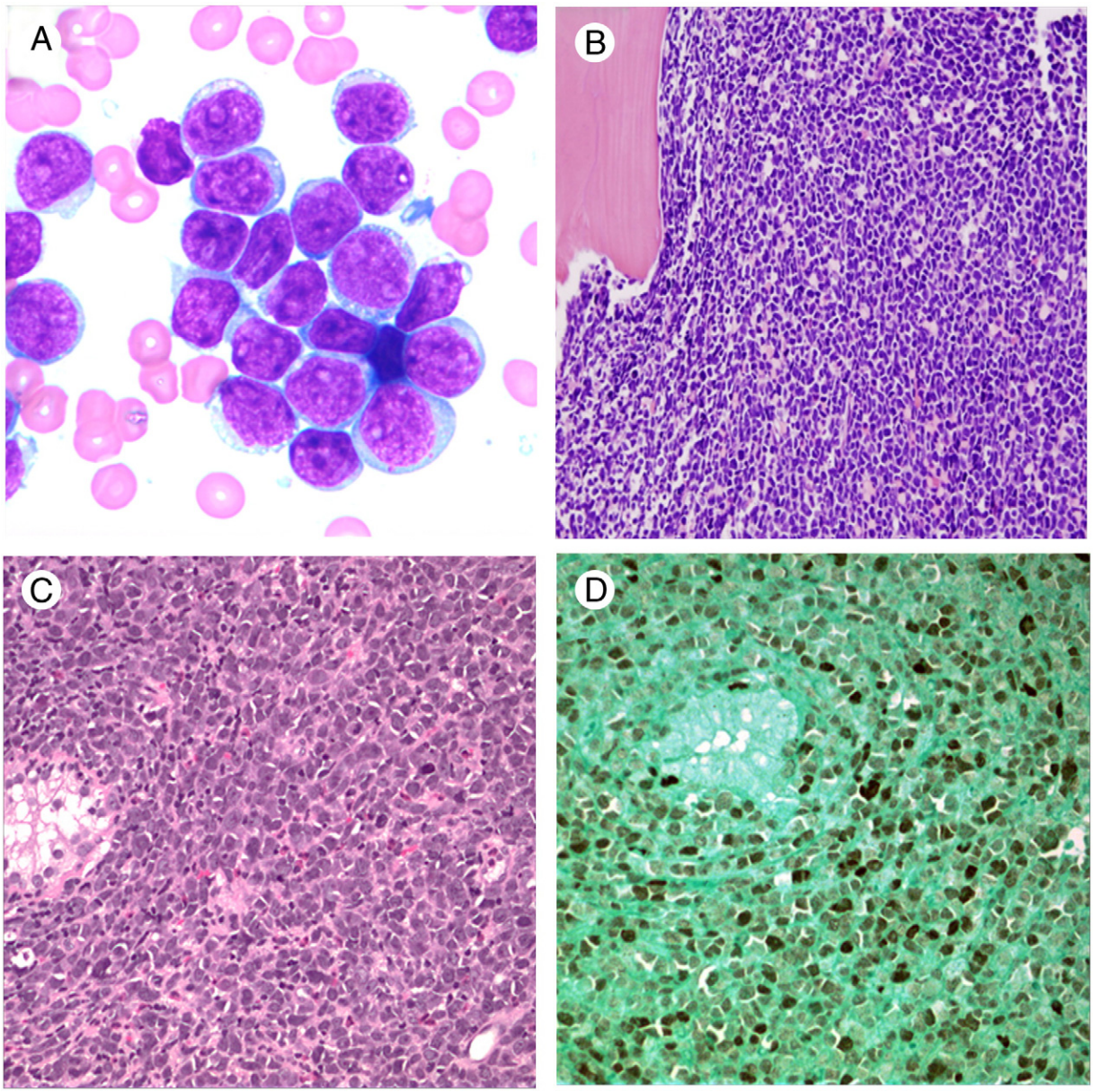


**Fig. 1** Representative morphologic and IHC findings in B-ALL. A, L1-type blasts, some with scant azurophilic granules. B, Diffuse infiltrate replacing bone marrow medullary space. C, B-ALL involving testis. D, IHC stain with TdT.