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ACUTE LYMPHOCYTIC LEUKEMIAS (K BALLEN AND M KENG, SECTION EDITORS)

Updates in the Pathology of Precursor Lymphoid Neoplasms in the Revised Fourth Edition of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues

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Abstract

Purpose of Review Acute lymphoblastic leukemias (ALL) are malignant disorders of immature B or T cells that occur characteristically in children, usually under the age of 6 (75%). Approximately 6000 new cases of ALL are diagnosed each year in the USA, 80–85% of which represent B-ALL forms. Most presentations of B-ALL are leukemic, whereas T-ALL presents with a mediastinal mass, with or without leukemic involvement. The revised fourth edition of the World Health Organization (WHO) classification (2017) has introduced some changes in both B and T-ALL. Here, we summarize the categories of lymphoblastic leukemia/lymphomas as defined by the WHO and recent developments in the understanding of this group of hematologic malignancy.

Recent Findings Two provisional categories of B-ALL have now been identified including B-ALL, *BCR-ABL1*-like, and B-ALL with iAMP21. The Philadelphia chromosome-like B-ALL includes forms of the disease that shares the expression profiling of B-ALL with *t*(9;22) but lack such rearrangement. The second one shows amplification of part of the chromosome 21. Both entities are associated with worse prognosis. Within the T-ALL group, an early precursor T cell form has now been introduced as a provisional category. Such group demonstrates expression of stem cell and myeloid markers in conjunction with the T cell antigens.

Summary The current review summarizes the recent updates to the WHO classification.

Keywords Lymphoblastic lymphoma · ALL · WHO revision · Acute leukemia

Introduction

Acute lymphoblastic leukemias (ALL) are malignant disorders of immature B or T cells that occur characteristically in children, usually under the age of 6 (75%) [1••, 2, 3•, 4]. Approximately 6000 new cases of ALL are diagnosed each year in the USA, 80–85% of which represent B-ALL forms. There is an increased incidence of ALL in children with Down's syndrome [5–7] and other constitutional genetic disorders. Recent genome-wide studies have shown that certain single nucleotide polymorphisms (SNPs) of genes (*GATA3*, *ARID5B*, *IKZF1*, *CEBPE*, *CDKN2A/B*) are associated with an increased risk of ALL [8]. However, familial forms of ALL are very rare and typically associated with mutations in the *PAX5* [9], *ETV6* [10], and *TP53* [11] genes. T-ALL is also prevalent in children, typically in association with a large mediastinal mass, often lacking peripheral blood or bone marrow involvement [12].

Clinically, many of the patients with B-ALL present with peripheral blood cytopenias. The leukocytes can be increased, normal, or decreased. Lymphadenopathy and hepatosplenomegaly are common. It is common to encounter bone pain and constitutional symptoms in children [2, 3•]. The diagnostic basis of lymphoblastic leukemia/lymphoma (ALL/LBL) remains the detection of B- or T-lymphoblasts in an extramedullary site or the presence of increased lymphoblasts (> 20%) in the bone

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marrow. The term acute lymphoblastic leukemia is reserved for cases with blood and bone marrow involvement, while cases presenting as a mass lesion without significant bone marrow involvement are referred to as lymphoblastic lymphoma (LBL). Although no definitive lower limit exists regarding the minimum percentage of lymphoblasts in the peripheral blood or bone marrow required to diagnose ALL, a fraction of 20% or greater is recommended by the *WHO* before making the diagnosis [3•, 12]. However, in cases where there is a mass and circulating lymphoblasts, a cutoff of 25% lymphoblasts (in the bone marrow sample) is frequently used in clinical trials to distinguish between "lymphoma" and "leukemia" [13].

The term B-ALL must not be used to indicate cases of Burkitt lymphoma with peripheral blood involvement. Recently, case reports of cases of B-ALL with *MYC* rearrangements have been reported [14, 15]. Cases of B-ALL with recurrent cytogenetic aberrations should be classified in accordance with the genetic alterations, rather than using the terminology of B-ALL, NOS [16].

The blasts in lymphoblastic leukemia may be small to large, with scant or moderate amounts of gray-blue cytoplasm which may be vacuolated (Figs. 1 and 2). Chromatin is finely dispersed and shows nucleoli. Caution is advised when interpreting blast cytoplasm to discern lineage, as a significant subset of ALL/LBL blasts may show coarse azurophilic granules which may mimic the primary granules seen in myeloid blasts [17, 18]. T- and B-lymphoblasts cannot be reliably distinguished from each other in smear preparations. In tissue sections of bone marrow or extramedullary sites, T-ALL/LBL often shows a higher frequency of mitoses than B-ALL/LBL, and T-LBL may histologically mimic Burkitt lymphoma [19, 20].

Distinction of B versus T cell lineage is done by immunophenotyping the lymphoblasts by flow cytometry or immunohistochemistry. Polymerase chain reaction studies of *IGH* and/or T cell receptor genes do not define the lineage specificity of ALL/LBL, as a majority of B-ALL/LBL and a significant minority of T-ALL/LBL may show clonal rearrangements of both *IGH* and T cell receptor genes [21].

B-Lymphoblastic Leukemia/Lymphoma

B-Lymphoblastic leukemia/lymphoma (B-ALL/LBL) accounts for the majority of cases of ALL in both children and adults. However, it accounts for only approximately 10% of cases of LBL, in which T-LBL predominates [22].

The immunophenotype characteristic of B-lymphoblasts includes positivity for CD19, cytoplasmic CD79a, PAX-5,TdT, CD10, and cytoplasmic CD22 (Fig. 3). Variable expression of CD20, CD34, and CD24 is present. B-Lymphoblasts commonly demonstrate a low level of CD45 expression (and sometimes complete negative expression) [3•]. While the 2008 *WHO Classification* excludes MPO-positive acute leukemias from the category of ALL, the 2017 revised fourth edition now acknowledges that rare cases may demonstrate positivity for myeloperoxidase by immunohistochemistry or flow cytometry [23, 24]. This group appears to have an increased risk of relapse and worse event-free survival.

Distinguishing between pro-B ALL (CD19+, cCD79a+, cCD22+, TdT+), common B-ALL (CD10+), and pre-B ALL(cμ chain+) is based on the immunophenotype, and morphologic correlations are not emphasized. It is always important to distinguish B-lymphoblasts from hematogones (B cell precursors). Hematogones show a continuum of expression of markers of B cell differentiation. Hematogones are typically bright for CD81 and CD38 [25–27]. Clonal rearrangements of the IGH are nearly always present in B-ALL and can sometimes be accompanied by T cell receptor rearrangements (up to 70% of cases) [21]. A recent subset of B-ALL have been shown to carry a *t*(17;19)(q22;p13.3) translocation creating a *TCF3-HLF* transcript. Such cases are very aggressive clinically and have not yet been incorporated as part of the groups of B-ALL with recurrent cytogenetic abnormalities [28, 29].

B-ALL has a relatively good prognosis in children (complete remission in > 95% of cases) and variable in adults (60–85% of complete remission). Eighty percent of children with B-ALL are cured, a significant change in mortality and outcome compared to what was seen approximately 20–

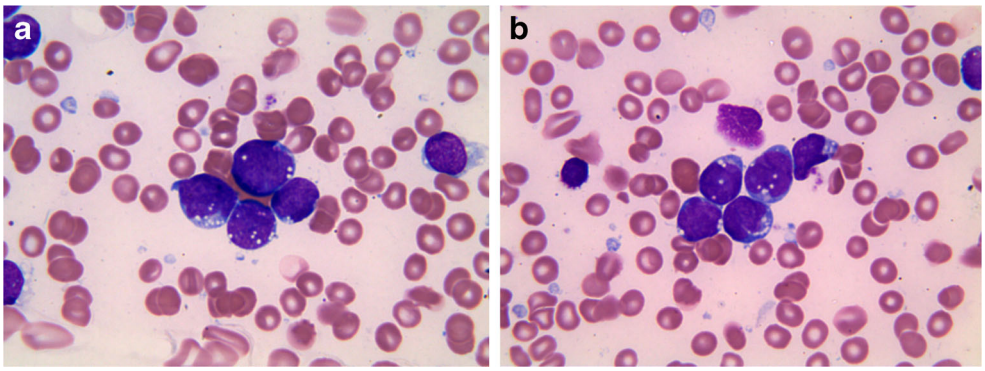

Fig. 1 B-ALL. Characteristic small lymphoblasts with scant cytoplasm, cytoplasmic vacuoles, and prominent nucleoli (**a**, **b**)

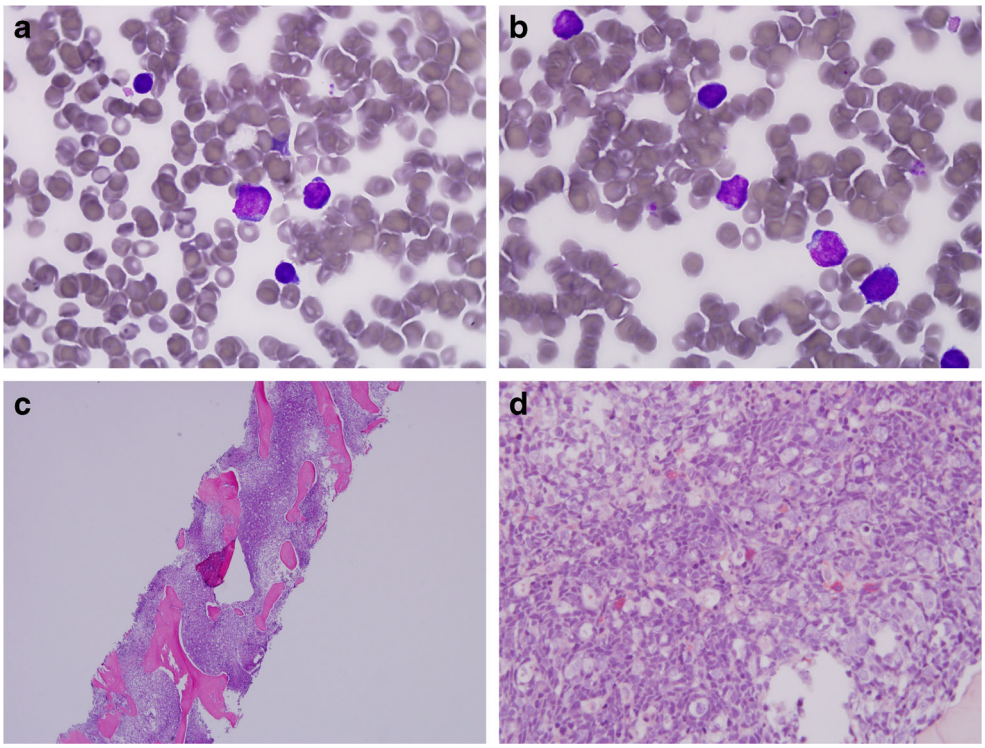

Fig. 2 B-ALL. Small lymphoblasts that lack vacuoles (**a**, **b**). The bone marrow shows extensive replacement by the population of immature cells (**c**, **d**)

30 years ago [30, 31]. Some factors can be associated with a worse prognosis: infant age at presentation, older age, higher white blood cell (WBC), presence of minimal residual disease (MRD), CNS involvement at presentation, hypodiploidy, etc. [31] (Fig. 4).

B-Lymphoblastic Leukemia/Lymphoma with Recurrent Genetic Abnormalities

Cytogenetics remains critical to the accurate diagnosis, subcategorization, and risk stratification of B-ALL/LBL. In the

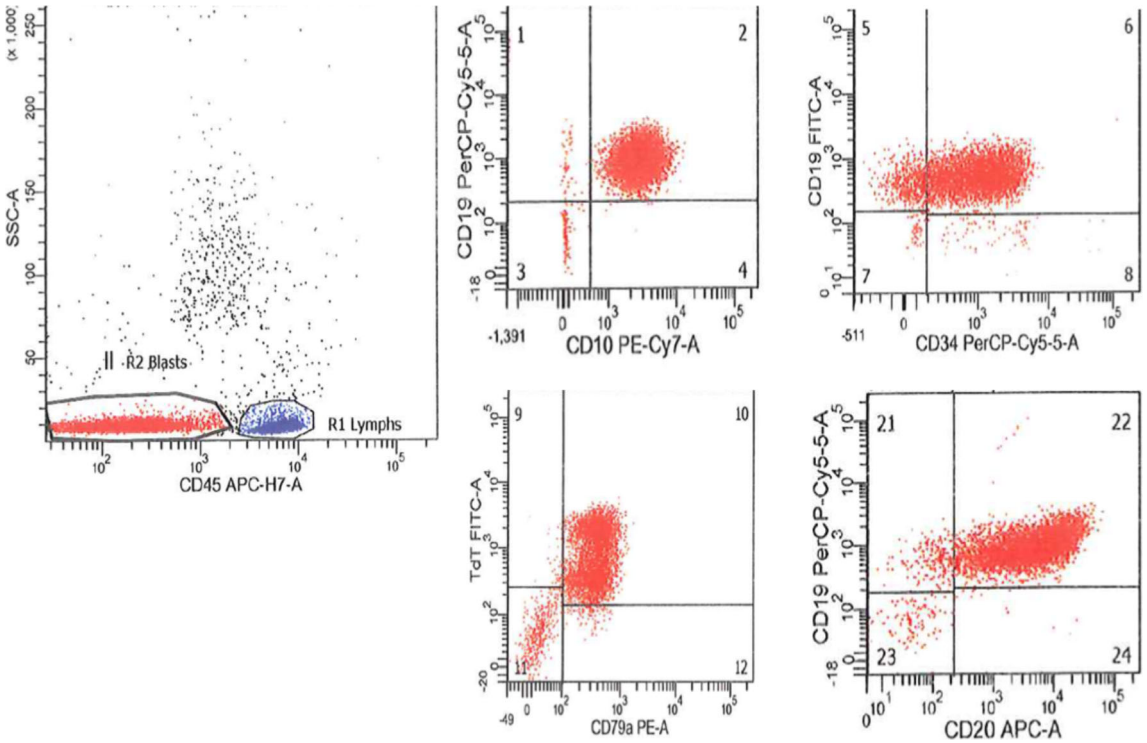

Fig. 3 B-ALL, immunophenotypic findings. The B-lymphoblasts are CD19+, CD34+, CD10+, TdT+, CD79a+, and CD20+

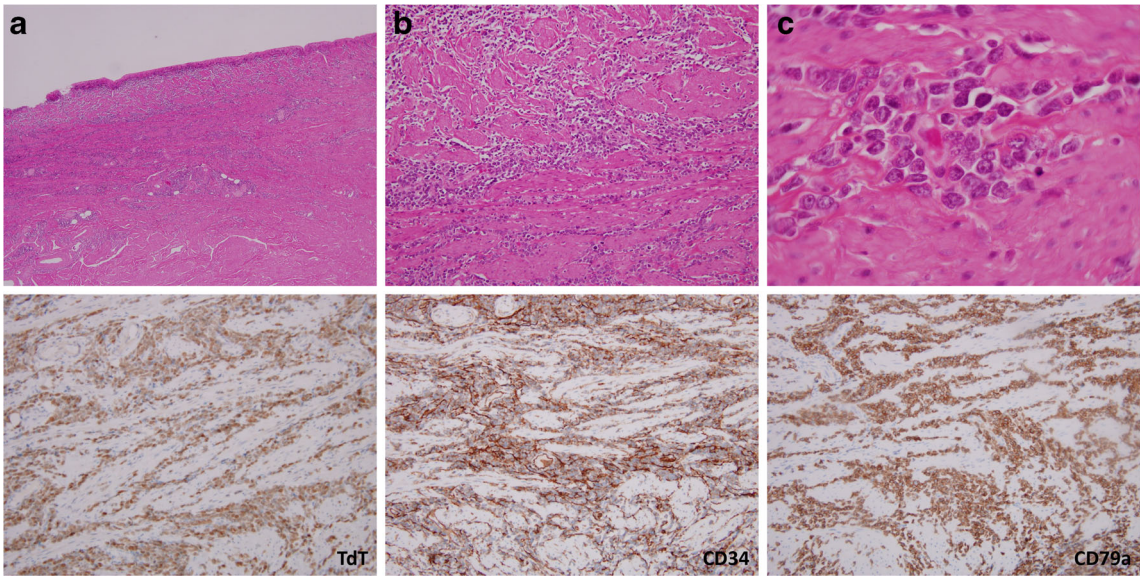

Fig. 4 Extranodal involvement in B-ALL. In this case, the lymphoblasts extend into the submucosa and muscularis wall in a cervical biopsy (**a**–**c**). They are CD79a+, TdT+, and CD34+

area of B-ALL/LBL with recurrent genetic abnormalities, the revision to the *WHO Classification* includes two additional subgroups not featured previously: B-ALL, *BCR-ABL1*-like, and B-ALL, with iAMP21 [16]. The subgroups included under this category in the revision are as follows (Table 1):

B-ALL with t(9;22)(q34;q11.2);*BCR-ABL1*
B-ALL with t(v;11q23); *KMT2A* rearranged [formerly *MLL*]
B-ALL with t(12;21)(p13;q22.1); *ETV6-RUNX1* [formerly *TEL-AML*]
B-ALL with hyperdiploidy
B-ALL with hypodiploidy
B-ALL with t(15;14)(q31.1;q32.1); *IGH/IL3*
B-ALL with t(1;19)(q23;p13.3); *TCF3-PBX1*
B-ALL, *BCR-ABL1*-like [new]
B-ALL with iAMP21 [new]

No significant changes were made in the subgroup with ***t*(9;22)(q34.1;q11.2);*BCR-ABL1*** which remains defined by the presence of a translocation *t*(9;22) resulting in *BCR-ABL1* fusion (Fig. 5), which may be the p210 or p190 transcript. They account for 25% of cases of B-ALL and adults and a smaller proportion of pediatric cases (2–4%) [32]. When this subtype presents in kids, it is considered as a high-risk factor [33]. The phenotype (CD19+,CD10+,TdT+) is characterized by the frequent coexpression of the myeloid markers CD13 and CD33, and CD25 in adults [34, 35].

The subgroup with ***t*(v;11q23)** resulting in rearrangement of ***KMT2A*** (formerly *MLL*) includes the many translocation partners of the "promiscuous" oncogene, with *KTM2A-AFF1* (formerly *MLL-AF4*) fusion being associated with a worse prognosis (Fig. 6) [2, 36, 37]. This is the most common subtype in infants < 1 year [33]. High WBC (> 100×10^9/l) and CNS involvement is typical. Their immunophenotype differs from B-ALL NOS in that the blasts are CD19+, CD10−, CD24−, and CD15+. There are more than 100 fusion partners that have been reported [38–40]. In addition to *AFF1*, other common partners include *MLLT1 (ENL)* and *MLLT3 (AF9)*. *KMT2A* rearranged ALLs are one of the cancer subtypes with the lowest numbers of additional mutations [2, 41]. They all share an extraordinary poor prognosis with dismal rates of cure rates, particularly in those < 6 months.

The subgroup of B-ALL with ***t*(12;21)(p13.2;q22.q); *ETV6-RUNX1***(formerly *TEL-AML1*) is essentially unchanged in the revised fourth edition and accounts for 25% of B-ALLs in children. The phenotype is similar to other B-ALL NOS (CD19+, CD10+, CD34+) and shows expression of CD13. This subtype carries a very good prognosis with cures in > 90% of cases [2, 42, 43].

Hyperdiploid cases are defined by the presence of more than 50 chromosomes within leukemic cells, most commonly in the absence of structural cytogenetic changes (Fig. 7). Such cases have a cure rate of > 90% on children (the prognosis in adults has not been adequately studied) [31, 44–46]. Care must be taken to avoid confusion with hypodiploid B-ALL with endoreduplication; true hyperdiploid cases typically have < 66 chromosomes [47]. Fluorescence in situ hybridization (FISH) may be useful in identifying hypodiploid chromosomes in such cases, and the discrepancy with karyotyping should raise the possibility of endoreduplication in a hypodiploid clone. The most common numerical gains occur in chromosomes 21, X, 14, and 4. Cases with concomitant trisomies

Table 1 Summary of recurrent cytogenetic abnormalities, immunophenotypic findings, and prognostic features in B-ALL

Defining cytogenetics	Locus involved	Cytogenetic versions/ variants	Special features	Associated immunophenotypes	Epidemiology	Relative prognosis
t(9;22)(q34;q11.2)	*BCR-ABL1*	May have other lesions in addition to *t*(9;22)	*Adults:* p190 or p210 transcript *Children:* p190 most common	CD10+, CD19+ TdT+, CD25+ Frequent CD33+, CD13+	Primarily adults	Very unfavorable
t(v;11q23)	*KMT2A (MLL)*	Many fusion partners; most commonly *AFF1* on 4q21. In infants, *t*(v;11q23) is typically only lesion	Frequently associated with *FLT3*	CD19+, CD15+ CD10−, CD24−	Seen in infants, adults	Unfavorable
t(12;21)(p13;q22.1)	*ETV6-RUNX1*	None	Unique gene expression profile	CD19+, CD10+, CD34+, CD13+, CD20−, CD9−	Children; rare in infants/adults	Very favorable
Hyperdiploidy	N/A	> 50 chromosomes Usually > 66 chromosomes; 4, 14, 21, and X are most common polysomies	Cytogenetics must exclude hypodiploid endoreduplication	CD19+, CD10+, CD34+ Often CD45−	Primarily children; not seen in infants; uncommon in adults	Very favorable
Hypodiploidy	N/A	< 46 chromosomes Near-haploid: 23–29 Low hypodiploid: 33–39 Near diploid: 44–45	Endoreduplication may cytogenetically mimic haploid/diploid	CD19+, CD10+	Uncommon across age groups; near-haploid seen in children	Unfavorable; near haploid is very unfavorable
t(15;14)(q31.1;q32.1)	*IGH/IL3*	None	Eosinophilia	CD19+, CD10+	Rare across age groups	Uncertain
t(1;19)(q23;p13.3)	*TCF3-PBX*	*t*(17;19) *TCF3-HFL* is associated with a very unfavorable prognosis	A *t*(1;19) not involving *TCF3-PBX* seen in other B-ALLs	CD19+, CD10+, CD34−, CD9 strong +, cytoplasmic μ +	Seen in children; uncommon in adults	Somewhat unfavorable
BCR-ABL1-like	Lacks *t*(9;22) *BCR-ABL1*	*CRLF2* translocations; EPOR translocations; *ABL1* translocations with non-*BCR* partners	Gene expression profile is similar to *BCR-ABL1* B-ALL Often associated with *JAK2 JAK1* mutations	CD19+, CD10+; *CRLF2* protein product is expressed in cases with translocation	Children; Down's syndrome; Hispanic/Native American heritage	Unfavorable overall
iAMP21	Partial amplification of chromo-some 21	Alterations of chromsomes 7 and X; loss of *RB1, ETV6; CRLF2* translocations	Detectable with probes to *RUNX1*, ≥ 5 in one cell or ≥ 3 on one chromosome 21	Not well-defined	Relatively rare; seen in older children	Unfavorable

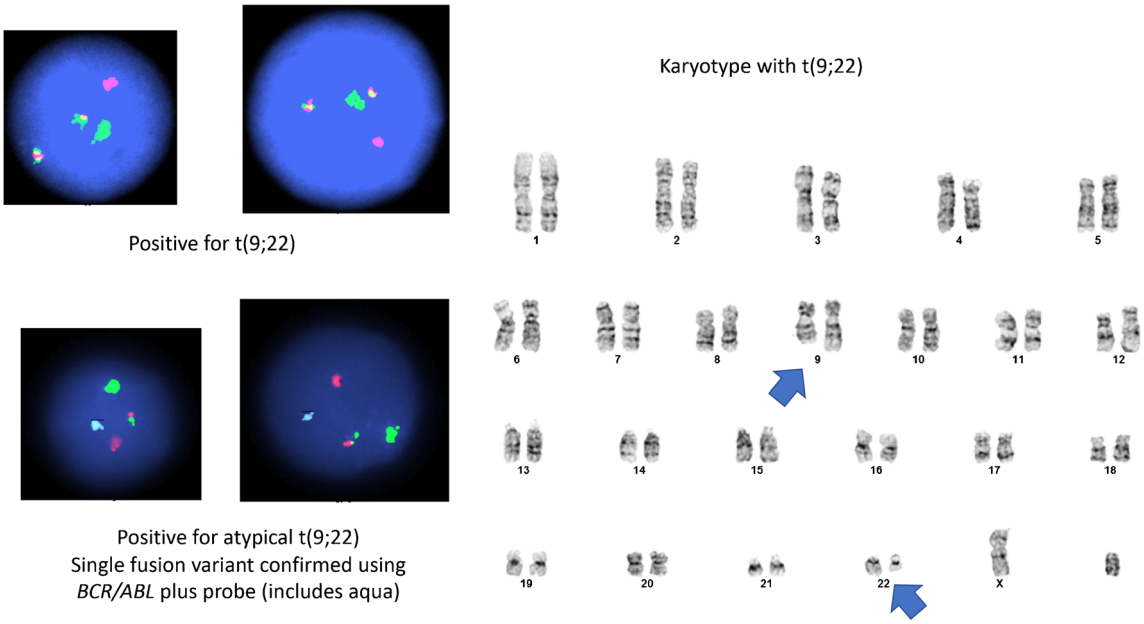

Fig. 5 B-ALL with *t*(9;22). The FISH panels are on the left side, and the karyotype is on the right. This is the B-ALL with a Philadelphia chromosome, and often a p210 isoform

of chromosomes 4 and 10 are believed to have the most favorable prognosis in this subgroup [48, 49]. They also account for 25% of B-ALL cases in children, but only 7–8% in adults.

Hypodiploid B-ALL is defined by the presence of fewer than 46 chromosomes in the leukemic cells and accounts for 5% of B-ALL cases. In the revised fourth edition, it has been further categorized into near-haploid (23–29 chromosomes), low-hypodiploid (33–39 chromosomes), high-hypodiploid (40–43 chromosomes), and near-diploid (44–45 chromosomes) [44, 50, 51]. Near-haploid cases are limited to childhood [50, 51]. Although no mention is made in the revised fourth edition of cases with 30–32 chromosomes, others have variably placed cases in this range within the near-haploid or low-hypodiploid subcategories [1, 2]. The near-haploid category carries the worst prognosis of this subgroup and is associated with *RAS* and receptor tyrosine kinase (*RTK*) mutations. Low hypodiploid B-ALL show loss-of-function mutations in *TP53* (including Li-Fraumeni syndrome germline mutations) and/or *RB1* in most cases [52]. The near-diploid category carries the best prognosis of cases of hypodiploid B-ALL.

Essentially, no changes were made to the subgroup of B-ALL with ***t*(5;14)(q31.1;q32.1); *IGH-IL3***, which is

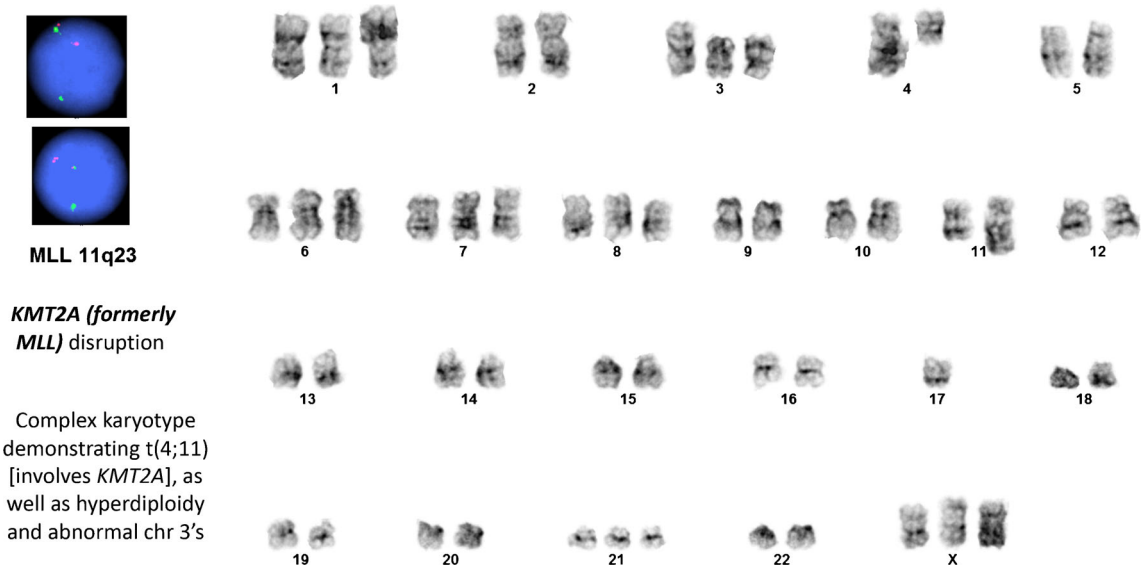

Fig. 6 B-ALL with *KMT2A* (formerly *MLL*) translocation, complex karyotype, and hyperdiploidy. The FISH panels are on the left side, and karyotype on the right side

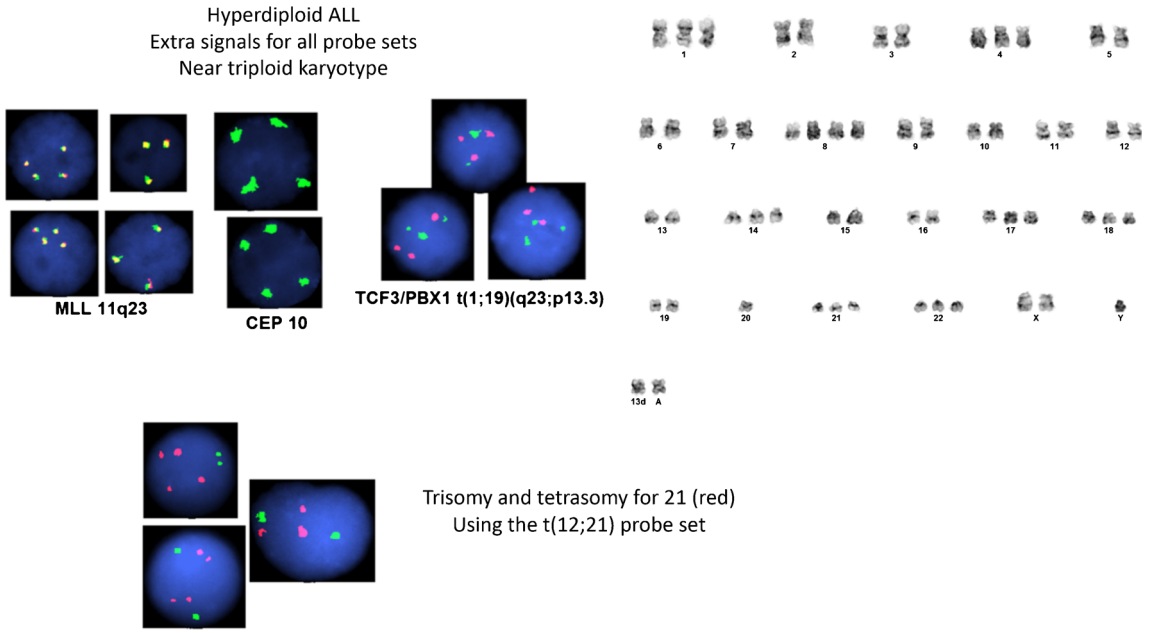

Fig. 7 B-ALL, hyperdiploidy. Copy number gains by FISH are present using the loci for MLL, CEP10, TCF3/PBX1, and CEP21. The karyotype on the right detects extrachromosomes 1, 4, 8, 14, 17, 18, 21, and 22

associated with eosinophilia and a frequently low blast percentage in the bone marrow. They account for < 1% of B-ALL cases. The prognosis is similar to other subtypes of B-ALL, NOS. The finding of even small number of blasts in association with eosinophilia is strongly suggestive of this diagnosis [16, 53].

B-ALL with ***t*(1;19)(q23;p13.3); *TCF3-PBX1*** includes the alternate translocation *t*(17;19) *TCF3-HLF* [28]. They account for 6% of cases of B-ALL and appear to be less frequent in adults. They frequently show *PAX-5* mutations [54]. They were originally thought to have a poor prognosis and increased risk of CNS involvement. However, with the novel regimens, its prognosis appears to be similar to other B-ALL cases [55]. This subgroup may be confused with B-ALL demonstrating an alternate but karyotypically identical *t*(1;19) which does not cause fusion of *TCF3 (formerly E2A)* and *PBX1*. Such cases can be distinguished immunophenotypically from *TCF3-PBX1* B-ALL, which is CD34-negative and strongly CD9-positive. Many cases of B-ALL with *t*(1;19) *TCF3-PBX1* show expression of BCL-6 [56]. The *TCF3-HLF* cases have a dismal prognosis [28].

B-ALL, *BCR-ABL1*-like was added as a provisional entity to the revised fourth edition of the *WHO Classification* [16]. This group of leukemias lacks a Philadelphia chromosome but shows gene expression profiles which mimic *BCR-ABL1*-positive B-ALL [57, 58]. *CRLF2* is translocated in approximately half of cases, and less frequently rearrangements leading to the truncation and activation of EPOR are seen [59]. They account for 10–25% of B-ALL cases, and their risk is increased in patients with Down syndrome. Its frequency is lowest among children with standard risk B-ALL, and higher in children with high-risk, adolescents, and adults. *CRLF2* is typically juxtaposed with *P2RY8* or *IGH*. They often show an interstitial deletion of the PAR1 gene family on Xp22.2 and Yp11.3 [60, 61]. Approximately half of cases with *CRLF2* translocation also demonstrate mutant *JAK2* or *JAK1*. Other frequently mutated genes include *IKZF1* and *CDKN2A/B* [62]. Of note, the protein product of *CRLF2* translocation is strongly expressed by the leukemic cells and is detectable by flow cytometry with reportedly high sensitivity. Other translocations involve juxtaposition of *ABL1* with a variety of partners other than *BCR (ABL2*, *PDGFRB*, *NTRK3*, *TYK2*, *CSF1R*, and *JAK2)* [61–63]. Pediatric cases with *PDGFRB* translocation have been associated with resistance to induction chemotherapy, but dramatic responses to tyrosine kinase inhibitors imatinib and desatinib. Many of the translocations seen in this subgroup of B-ALL are not detected by routine karyotyping. Its phenotype is typical for classic B-ALL cases (CD19+, CD10+). It is associated with a poor prognosis, higher risk of being MRD+, and high WBC at presentation [64–66].

B-ALL with iAMP21 is the second new entity in the category of B-ALL with recurrent genetic abnormality. It is characterized by amplification of part of chromosome 21, which can be detected by FISH with specificity for the amplified region showing five or more total copies of the target, and/or three or more copies located on a single chromosome (Fig. 8) [2, 67]. This is more common in children and account for 2% of B-ALL cases [67–69]. Probes for *RUNX1* may be used for this purpose, although the content of gene itself is unaffected. This subgroup of B-ALL has been associated with a constitutional Robertsonian translocation rob(15;21)(q10;q10), which confers a 3000% increase in risk. It has also been associated with translocations

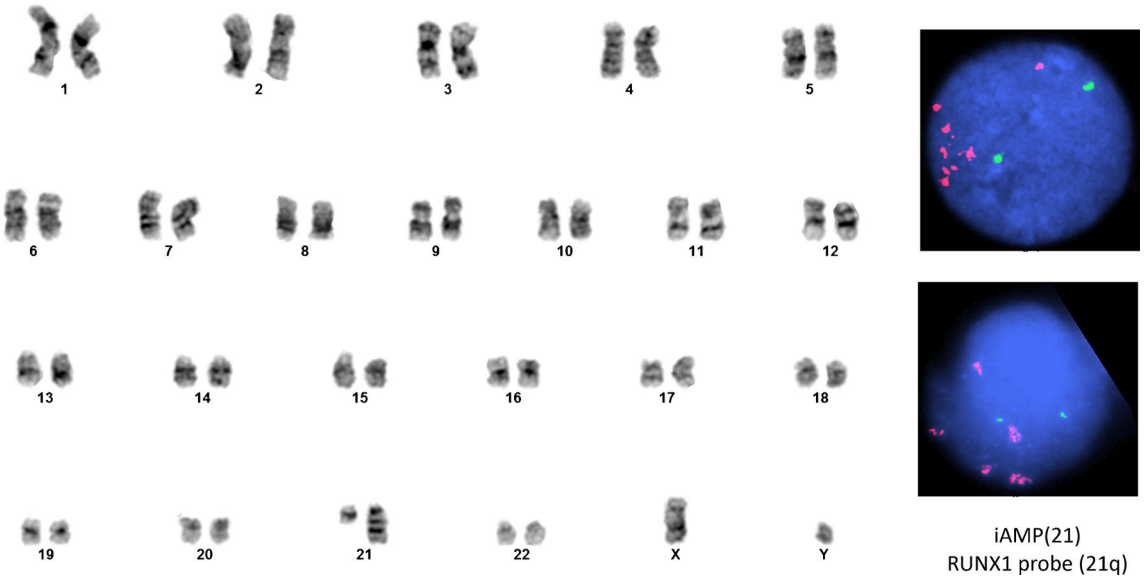

Fig. 8 B-ALL, iAMP(21). Amplification of the *RUNX1* locus is noted

of *CRLF2*, in which case the translocation subordinated to the cytogenetically more unique iAMP21. The immunophenotype is not specific. Eighty percent of these cases also have gains of chromosomes X and 7. This subtype carries a poor prognosis and requires more intensive therapy [67, 70–73]. *RAS* mutations are present in approximately 60% of cases [74].

T-Lymphoblastic Leukemia/Lymphoma

T-lymphoblastic leukemia/lymphoma (T-ALL/T-LBL) accounts for only a minority of cases of ALL, from approximately 15% of pediatric cases to 25% of adult cases. However, it accounts for around 90% of cases of LBL [12]. Unlike myeloid leukemias, there are no established criteria (e.g., > 20%) to establish a diagnosis of T-ALL. Unlike B-ALL, aleukemic presentations in the setting of bone marrow involvement are very unusual. The classic clinical presentation is of a mediastinal mass in a young individual [75, 76]. In addition to lymph nodes, the skin, tonsils, liver, spleen, CNS, and testes can also be involved. T-ALL in childhood is considered higher risk compared to B-ALL [77, 78]. The disease is associated with higher risk of induction failure, early relapse, and isolated CNS relapse [79]. Unlike B-ALL, WBC does not appear to be of prognostic significance. In adults, T-ALL has a similar or perhaps better prognosis compared to B-ALL [22].

Morphologically, the blasts are indistinguishable from those of B-ALL and can also have cytoplasmic vacuoles. However, they tend to be relatively small and sometimes show a more clumped character of the chromatin simulating more mature lymphocytes. The involved lymph nodes can show complete effacement of the architecture and in some cases affect the paracortical areas with sparing of germinal centers (Figs. 9 and 10) [12]. A "starry-sky" appearance mimicking Burkitt lymphoma has been identified. Cases with histologic findings of T-LBL, eosinophilia, myeloid hyperplasia, and an 8p11.2 cytogenetic aberration involving the *FGFR1* gene have been described as the "8p11 syndrome" [80, 81].

Immunophenotypically, T-ALL/T-LBL blasts are generally positive for TdT and cytoplasmic CD3, the latter being considered lineage-specific for T cells. CD1a, TdT, CD34, and/or CD99 positivity helps to categorize the cells as immature [12] (Fig. 11). The T-lymphoblasts show variable expression of other T cell markers (CD2, CD5, CD7). Many cases show coexpression of both CD4 and CD8. Some cases can express CD10, and, in those, careful evaluation for the *BCR-ABL* translocation is warranted [82]. Approximately 29–48% of cases show expression of TAL1 (but such does not correlate with *TAL1* fusions) [83, 84]. The aberrant TAL1 expression interferes with differentiation and proliferation by inhibiting like B-ALL. TAL1 overexpression in adults is associated with a worse prognosis. T-ALL may show aberrant expression of other markers, such as the B cell associated marker CD79a, and the myeloid markers CD13 and CD33. CD117 may also be positive, a finding which has been associated with *FLT3* mutation [85, 86]. Subcategorization of T-ALL/LBL by immunophenotyping is into pro-T, pre-T, cortical T, and medullary T. The pro-T and pre-T subcategories show double negativity of CD4 and CD8, while cortical T shows coexpression of CD4 and CD8 and medullary T shows expression of one or the other marker [87, 88]. T-ALL cases can lack surface expression of TCRαβ and TCRγδ, or show one of the two [89, 90].

Although several different recurrent cytogenetic and molecular abnormalities have been described in T-ALL/LBL, a separate category of T-ALL/LBL with recurrent genetic abnormalities is not a part of the revised fourth edition of the

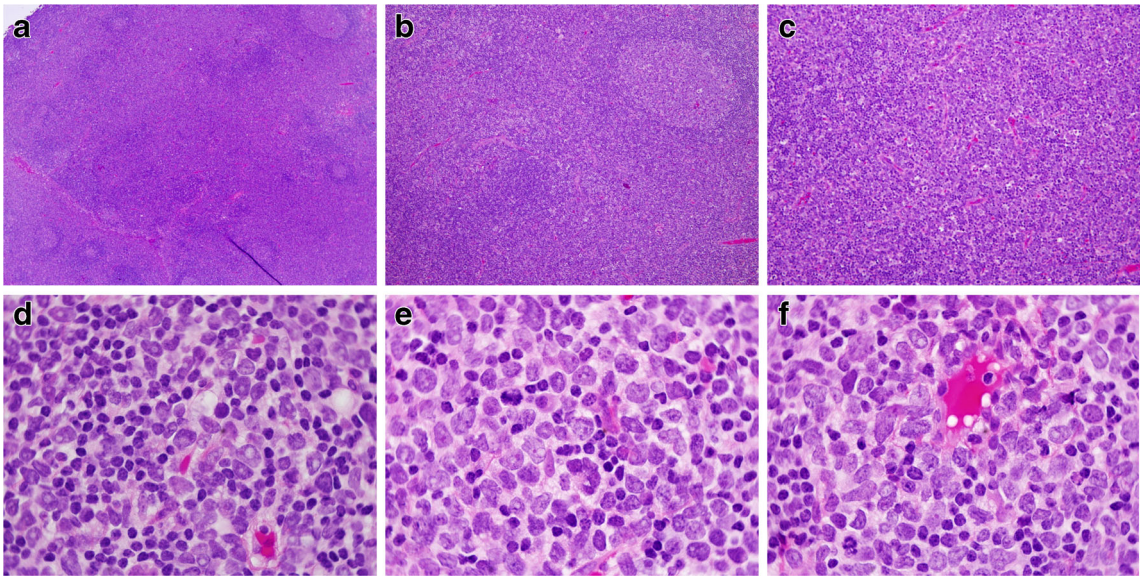

Fig. 9 T-LBL. Partial effacement of the lymph node with focally preserved germinal centers (**a**–**c**). The T-lymphoblasts occupy the paracortical areas of the lymph node. The T-lymphoblasts are medium in size and show fine chromatin, scant cytoplasm, and prominent nucleoli (**d**–**f**)

WHO Classification [79, 91, 92]. An abnormal karyotype is present in 50–70% of cases. The most common alterations involve the alpha and delta TR locus at 14q11.2, the beta locus at 7q35, and the gamma locus at 7p14–15. However, genetic subgroups of T-ALL/LBL with translocations leading to aberrant gene expression profiles have been described [84, 91, 92]. The proposed subgroups are listed according to the aberrant gene(s) expressed:

- *LMO* genes or *TAL1* at 1p32, and sometimes associated with *MYC* translocations [93]
- *TLX1* (formerly *HOX11*) at 10q24 (involved in 7% of T-ALL in childhood and 30% of adult cases) [94]
- *TLX3* (formerly *HOX11L2*) at 5q35 (involved in 20% of T-ALL in childhood and 10–15% of adult cases) [94]
- *HOXA* genes [95]

The LMO genes include *LMO1* at 11p15 and *LMO2* at 11p13 (formerly called *RBTN1* and *RBTN2*, respectively). *TAL1* translocation is relatively common, occurring in 20–30% of cases. The subgroup with aberrant *TLX1* has been associated with a relatively better prognosis [96]. Cases

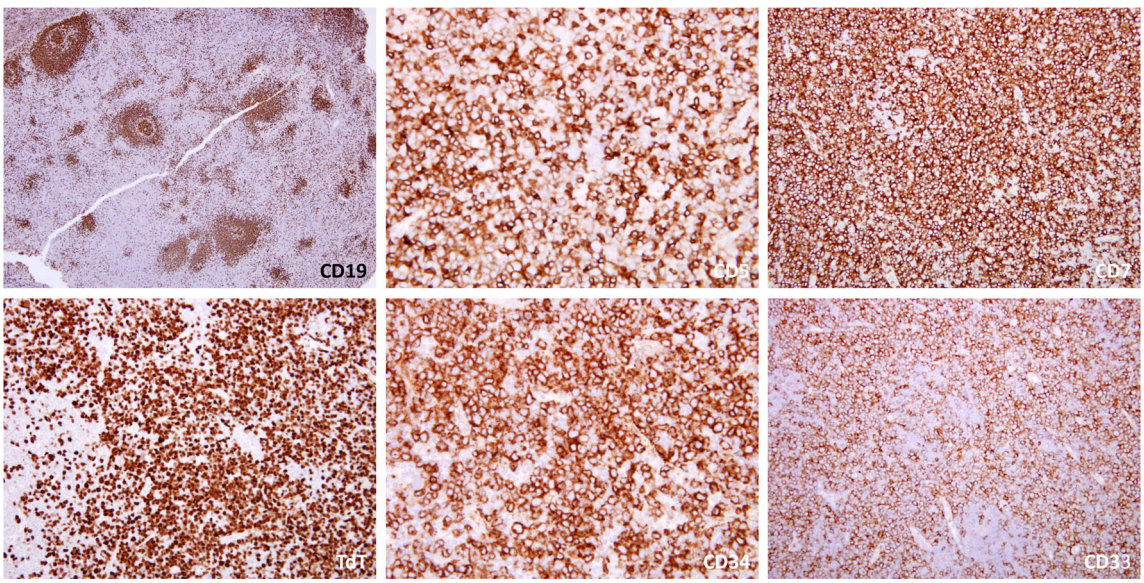

Fig. 10 T-LBL, immunophenotype. CD19 highlights the focally residual germinal centers. The immature blasts are positive for CD5, CD7, TdT, CD34, and CD33. In this particular example, this corresponds to a case associated with a 8p11 syndrome (frequent aberrant expression of myeloid markers)

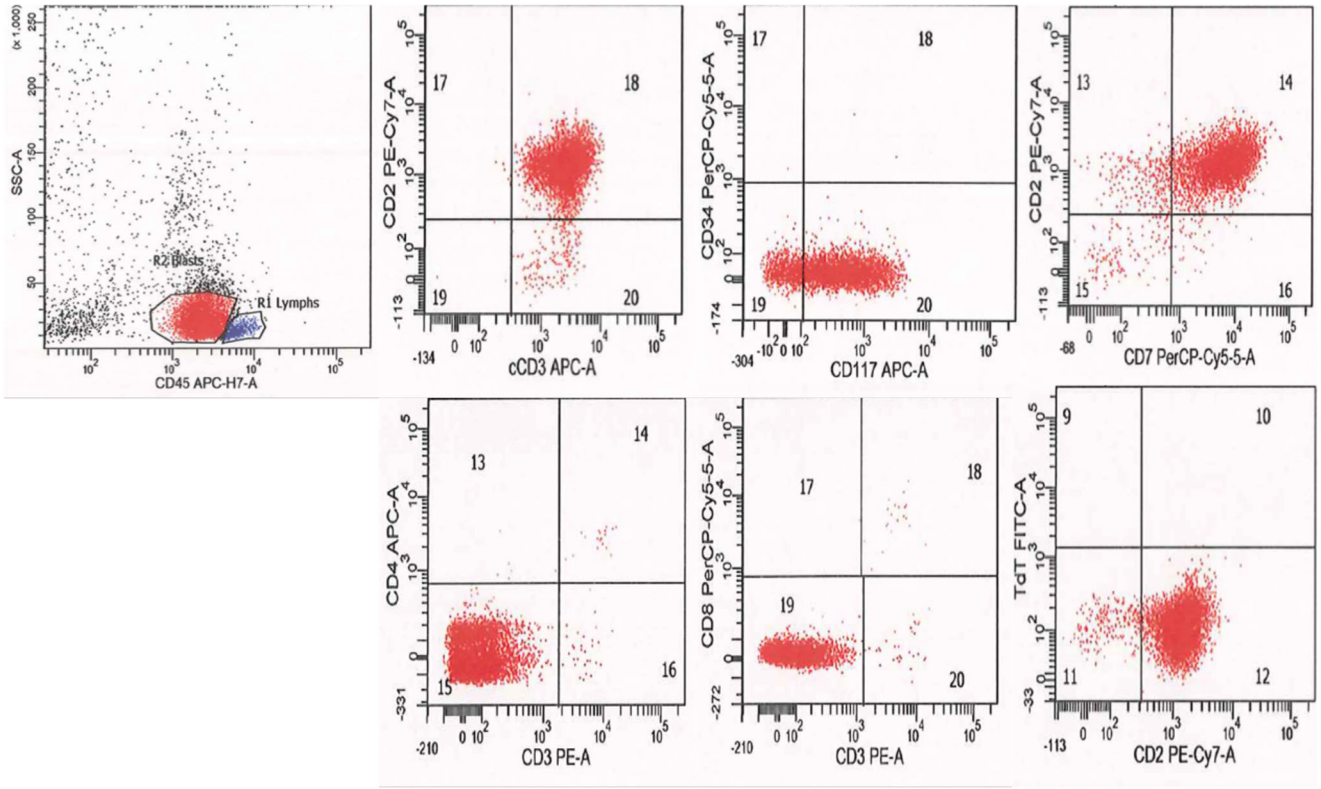

Fig. 11 T-ALL, immunophenotype. The T-lymphoblasts are cCD3+, CD2+, CD7+, CD117+, TdT−, CD4−, CD8−, CD34−

with activation of HOXA genes have shown translocations *t*(10;11)(p13;q14) resulting in *PICALM-MLLT10* fusion (10% of cases) and *KMT2A* (8% of cases) translocations. Although translocations are common in T-ALL/LBL, they are frequently cryptic and not detected by conventional cytogenetics.

Other structural abnormalities seen in T-ALL/LBL include deletions, mostly importantly del(9p) resulting in loss of *CDKN2A* which is seen in 17–30% of cases [97]. In addition, activating mutations of *NOTCH1* (a *MYC* effector) are seen in about half of cases and have been associated with a shorter survival in adult patients [98]. Approximately 30% of cases show mutations in the *FBXW7*, a feature that results in the increased half-life of the NOTCH1 protein [99].

Recently, cases of indolent T-lymphoblastic proliferations have been reported. Such cases involve the upper respiratory tract, have high local-recurrences, and lack systemic dissemination. Those cases are morphologically and immunophenotypically similar to T-LBL, but lack clonal rearrangements of TCR [100–103].

Early T Cell Precursor Lymphoblastic Leukemia

A new provisional entity in the revised fourth edition is early T cell precursor lymphoblastic leukemia (ETP-ALL), which accounts for 10–13% of pediatric T-ALL cases and 5–10% of adult cases [12]. The neoplastic cells demonstrate a characteristic immunophenotype, in which expression of stem cell and myeloid markers is seen with cytoplasmic CD3, CD7, CD34, CD117, HLA-DR, CD13, CD33, CD11b, and CD65. CD8 and CD1a are negative. CD2, CD4, and CD5 may or may not be expressed. Expression of CD123 appears to be relatively specific in this subtype [104]. MPO is not seen, as its expression in conjunction with the limited T cell antigen expression seen in the ETP-ALL phenotype would suggest instead a T/myeloid mixed phenotype acute leukemia. The prognosis of ETP-ALL appears to be similar to other forms of T-ALL provided that there is an intense treatment modality [105].

Gene expression profiling of ETP-ALL shows a profile similar to that of normal early thymocyte precursors [106]. The overexpressed genes include many that are associated with myeloid or early stem cell profile: *CD44*, *CD34*, *KIT*, *GATA2*, and *CEBPA*. Many cases that have been previously described with high expression of LYL1 represent examples of this particular subtype. ETP-ALL shows mutations which are more associated with myeloid than T cell leukemias, including *FLT3, DNMT3A*, *IDH1*, *IDH2*, and genes in the Ras family [107].

NK-Lymphoblastic Leukemia/Lymphoma

A new provisional entity in the revised *WHO Classification*, NK-lymphoblastic leukemia/lymphoma (NK-ALL/LBL), is

characterized by the proliferation of NK-cell progenitors but shows considerable antigenic overlap with T-ALL/LBL, making the diagnosis challenging [108]. These cells often lack CD16 but show expression of CD56, CD94, and CD161. Expression of CD56 is also seen in blastic plasmacytoid dendritic cell neoplasm, which must be excluded. *IGH* and TCR genes do not show evidence of mutation or rearrangement [109, 110]. The use of antigen panels against killer-cell immunoglobulin-like receptors (KIRs) may be helpful in establishing NK-cell identity but is not widely available.

Summary

These changes to the classification of T- and B-lymphoblastic leukemia/lymphoma in the revised fourth edition of the WHO reflect primarily a better understanding of the prognostic implications of certain cytogenetic and molecular alterations which did not previously define separate subcategories, as well as the addition of rare entities which were not categorized in the previous classification. For B-ALL, the major updates include the addition of *BCL-ABL1*-like and iAMP22 subsets, both of which are associated with a poorer prognosis, the former being detectable with FISH probes against *RUNX1* and the latter being detectable with gene expression profiling. In T-ALL/LBL, the major changes include the addition of early T cell precursor lymphoblastic leukemia (ETP-ALL) and NK-lymphoblastic leukemia/lymphoma.

Compliance with Ethical Standards

Conflict of Interest Christopher Wenzinger and Eli Williams declare that they have no conflicts of interest. Alejandro A. Gru, M.D. has consultant and advisory board relationships with Seattle Genetics and Bristol-Myers Squibb.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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