2016 Revision to the WHO classification of acute lymphoblastic leukemia

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B CELL ACUTE LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

Two important new provisional entities have been recognized in B cell acute lymphoblastic leukemia/lymphoma (B-ALL) with recurrent genetic abnormalities, which are titled as Intrachromosomal amplification of chromosome 21 (iAMP21) and BCR-ABL-like B lymphoblastic leukemia/lymphoma.

iAMP21 was defined as three or more extra copies of RUNX1 on a single abnormal chromosome 21 (a total of five or more RUNX1 signals per cell)^[1,2] with a complex structure comprising multiple regions of gain, amplification, inversion and deletion, identified from cytogenetics, fluorescence in situ hybridisation (FISH) and genomic analysis^[3] iAMP21 cases was originally identified in childhood acute lymphoblastic leukemia (ALL)^[4,5]. Prospective screening in recent childhood trials (Medical Research Council ALL97, United Kingdom (UK) ALL2003 and Children's Oncology Group (COG) ALL trials) has determined the incidence to be 2%. iAMP21 patients generally had low white cell counts (WCCs) with a median age of 9–11 years^[2,6] and had an inferior outcome when treated on standard therapy as compared with other patients treated on the same protocols^[1]. However, when iAMP21 patients treated as high risk showed improved outcome regardless of the backbone chemotherapy regimen given, indicating iAMP21 patients will to be treated as cytogenetic high risk, receive intensive chemotherapy.

The BCR-ABL-like ALL is another high-risk subtype. Genetic studies revealed

it had a high frequency of deletions in genes involved in B-cell development, including IKZF1, E2A, EBF1, PAX5 and et al, which was similar to the signature of BCR-ABL1-positive ALL^[7,8]. Common features of BCR-ABL1-like ALL include translocations involving other tyrosine kinases, or alternatively translocations involving either the cytokine receptor-like factor 2 (CRLF2), or, less commonly, rearrangements leading to truncation and activation of the erythropoietin receptor (EPOR)^[9]. Rearrangement of CRLF2 is associated with mutation of JAK kinases, particularly common in children with Down syndrome, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. The translocation results in upregulation of CRLF2 gene product, which can be detected by flow cytometry. The cases with translocations of tyrosine kinase genes involving ABL1 (with partners other than BCR), ABL2, PDGFRB, NTRK3, TYK2, CSF1R and JAK2, have shown remarkable responses to TKI therapy^[10], especially those with EBF1-PDGFRB translocations^[11]. Patients with BCR-ABL1-like ALL show a high frequency of alteration of IKZF1, a gene that encodes the lymphoid transcription factor IKAROS, but these deletions also occur in high frequency in other types of ALL as well^[8].

Another highlights is the unique association between low hypodiploid ALL and TP53 mutations that are often constitutional. The hypodiploid subgroup is heterogeneous and comprises ALL with a chromosome number of <46. By multiple whole genomic profiling of 124 hypodiploid ALL cases, inherited origin of the TP53 mutation was identified.^[12,13]

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T CELL ACUTE LYMPHOBLASTIC LEUKEMIA/ LYMPHOMA

A new pathologic entity in T cell acute lymphoblastic leukemia/lymphoma (T-ALL) is recognized as indolent T-lymphoblastic proliferation (iT-LBP). It typically involves lymphoid tissue of the upper aerodigestive tract but may occur in other locations and usually form a tumor mass. Microscopic features of involved lymph nodes shows these lymphoblasts localize predominantly to interfollicular/paracortical regions^[14–19], with less cytologically atypical features than the usual T-lymphoblastic lymphoma.

Its phenotype reflects a developmentally normal, non-aberrant phenotype and the proliferations are not clonal, indicating it is a non-neoplastic entity that may mimic T-lymphoblastic lymphoma and do not require treatment^[20].

The proposed Criteria for the diagnosis of an iT-LBP is as below (Table 1)^[20]:

iT-LBP have been associated with Castleman disease and/or follicular dendritic cell tumors and also been seen in cases of AITL and may persist in multiple lymph node sites even after clearance of AITL^[20,21].

ETP-ALL is a distinct pathobiologic entity confers a dire prognosis. The cell for clonal expansion is a very early immigrant from the bone marrow to the thymus, a cell expressing abundant T-lineage, stem-cell and myeloid-associated transcripts, and possessing both lymphoid and myeloid developmental potential^[22–26]. The specific immunophenotype of ETP-ALL is CD1-, CD5weak, CD8-, or coexpression of stem cell and/or myeloid markers CD34, CD117, HLADR, CD13, CD33, CD11b or CD65 and its distinct molecular features are FLT3 mutations and absence of NOTCH1 mutations^[27,28]. ETP-ALL was associated with an inferior clearance of leukemia cells after the first phase of remission induction therapy and extremely poor event-free and overall survival in patients

treated on intensified chemo- therapeutic protocols both at the St Jude Children's Research Hospital and the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)^[29].

Conflict of Interest

None declared.

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Table 1: Proposed Criteria for the diagnosis of an iT-LBP

Major criteria

1. TdT +/CD3 + T cells in sheets or dense clusters primarily in interfollicular regions;
2. Preservation of general follicular lymphoid architecture;
3. Small-sized to medium-sized T cells without significant morphologic atypia;
4. No aberrant antigen expression;
5. Nonclonal TdT + T cells;
6. No associated thymic epithelium
7. Clinical evidence of indolence, >6 mo follow-up without significant progression in the absence of treatment

Ancillary findings

Can be associated with Castleman disease and/or follicular dendritic cell tumors/sarcomas

Can be associated with patients with concurrent AITL or history of AITL (AITL indicates angioimmunoblastic T-cell lymphoma).

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