Best Practice & Research Clinical Haematology

Biopathology of Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma

--Manuscript Draft--

Manuscript Number:	
Article Type:	VSI: Childhood heme malignancies
Keywords:	pathobiology; genetic; childhood; adolescent and young adult; non-Hodgkin lymphoma,
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Abstract:	Mature non-Hodgkin lymphomas (NHL) in the childhood, adolescent and young adult (CAYA) population are rare and exhibit unique clinical, immunophenotypic and genetic characteristics. Application of large-scale unbiased genomic and proteomic technologies such as gene expression profiling and next generation sequencing (NGS) have led to enhanced understanding of the genetic basis for many lymphomas in adults. However, studies to investigate the pathogenetic events in CAYA population are relatively sparse. Enhanced understanding of the pathobiologic mechanisms involved in non-Hodgkin lymphomas in this unique population will allow for improved recognition of these rare lymphomas. Elucidation of the pathobiologic differences between CAYA and adult lymphomas will also lead to the design of more rational and much needed, less toxic therapies for this population. In this review, we summarize recent insights gained from the proceedings of the recent 7th International CAYA NHL Symposium held in New York City, New York October 20-23, 2022.

Biopathology of Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma

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Abstract

Mature non-Hodgkin lymphomas (NHL) in the childhood, adolescent and young adult (CAYA) population are rare and exhibit unique clinical, immunophenotypic and genetic characteristics. Application of large-scale unbiased genomic and proteomic technologies such as gene expression profiling and next generation sequencing (NGS) have led to enhanced understanding of the genetic basis for many lymphomas in adults. However, studies to investigate the pathogenetic events in CAYA population are relatively sparse. Enhanced understanding of the pathobiologic mechanisms involved in non-Hodgkin lymphomas in this unique population will allow for improved recognition of these rare lymphomas. Elucidation of the pathobiologic differences between CAYA and adult lymphomas will also lead to the design of more rational and much needed, less toxic therapies for this population. In this review, we summarize recent insights gained from the proceedings of the recent 7th International CAYA NHL Symposium held in New York City, New York October 20-23, 2022.

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Introduction

Mature lymphomas in childhood, adolescent and young adult (CAYA) population are rare and exhibit unique clinical, immunophenotypic and genetic characteristics. Research focused on the investigation of biopathologic features of NHL in CAYA population are relatively sparse. Enhanced understanding of the pathobiologic mechanisms involved in lymphomas in this unique population will allow for improved recognition of these rare lymphomas. Elucidation of the pathobiologic differences between CAYA and adult lymphomas will also lead to the design of more rational and much needed, less toxic therapies for this population. There is an unmet clinical need for improved understanding of the pathogenetic mechanisms that contribute to the unique biology of lymphomas especially in CAYA as it will allow for more tailored therapies that are less toxic with minimal long-term effects and enhance long-term survival and prevent development of secondary neoplasms. However, while it is well accepted that lymphomas in this population exhibit distinct biologic behavior from those of the adults, the World Health Organization (WHO) classification of lymphoid neoplasms only recently recognized distinct clinicopathologic subtypes that may arise in the pediatric population. Furthermore, while the basis of subclassification of adult NHL is centered around the concept of cell of origin and that lymphoma subtypes represent neoplastic counterparts of lymphocytes in different phases of differentiation, the immunologic milieu of lymphomas of the CAYA population is likely different from those of the adults but remain unexplored. Emerging recognition of B-, T-cell subsets with distinct immunologic function and differentiation profiles may also be different in children relative to adults. Third, several studies, albeit limited in number, have shown that the mutational burden and overall genomic complexity observed in pediatric neoplasms are significantly lower than those in adults. Additionally, most lymphomas in the CAYA population occur as *de novo* lymphomas while transformation events from low grade into aggressive forms are rare. Finally, there is unrecognized contribution of constitutional germline genetic abnormalities that may contribute to altered immune response and the pathogenesis of lymphomas in the pediatric population. In this review, we summarize recent pathobiogic insights presented at the proceedings of the 7th International CAYA NHL Symposium held in New York City, New York October 20-23, 2022.

The basic outline of the 5th Edition of the WHO Classification of Haematolymphoid Tumours has been published in 2022 (1) and is available in full text form as an online beta-version (https://www.iarc.who.int/) with the print version expected to be published as the "Blue Book" by IARC in 2023. The chapters on NHL lymphomas commonly observed in the CAYA population have been co-authored by hematopathologists, geneticists as well as by leading clinical experts in the field of CAYA lymphomas (many of whom were active participants of the CAYA NHL Symposium in New York City). The definitions, descriptions and essential and desirable diagnostic criteria of several common CAYA lymphomas have been refined and entities previously considered as provisional entities have been "upgraded" to definitive entities. The biopathologic features of the most common NHL in the CAYA population are outlined in the following sections.

Mature B-cell Lymphomas

Burkitt lymphomas (BL)

Burkitt lymphoma (BL) is a mature aggressive B-cell neoplasm with distinct histomorphologic features and of germinal center B-cell derivation exhibiting a high proliferation index (~100%) (1). Chromosomal translocations leading to juxtaposition of the MYC oncogene with one of the three immunoglobulin gene loci are the hallmarks of BL (2). The detection of such an IG::MYC translocation is not absolutely essential for the diagnosis of BL if strong MYC expression is documented in at least 80% of cells and other features are in line with its typical histologic and immunophenotypic characteristics. Nevertheless, documented absence of an IG::MYC translocation precludes the diagnosis of BL. In this regard, cryptic insertions of the IG regulatory sequence into the MYC locus or vice versa can be missed by commonly utilized techniques such as fluorescence in situ hybridization (FISH) (3). Moreover, application of only a MYC break apart probe can by definition not verify an IG::MYC fusion. A chromosomal breakpoint affecting the BCL2 locus should be absent. Its presence favours the diagnosis of Diffuse large B-cell lymphoma (DLBCL) /high grade B-cell lymphoma (HGBL) with MYC and BCL2 rearrangements. Similarly, chromosomal breakpoints affecting the BCL6 locus are mostly absent and favours the diagnosis of

Diffuse large B-cell lymphoma /high grade B-cell lymphoma (HGBL). The mutational landscape of secondary aberrations is highly conserved in BL and besides the MYC gene involves those encoding members of the ID3/TCF3 complex (4), the SWI/SNF complex (e.g. SMARCA4), cell cycle regulators (e.g. CCND3), BCR signaling and the TP53 gene. Comparative analyses of the mutational landscapes of EBV positive and negative BL demonstrate differences in mutational load rather than involved genes (5). Remarkably, these molecular differences which are obviously confounded by the geographical background favour a distinction into EBV-positive and negative lymphomas rather than into the epidemiologic variants of endemic and sporadic Burkitt lymphomas.

High-grade B-cell lymphomas with 11q aberrations

High-grade B-cell lymphomas with 11q aberrations represent a rare group of mature B-cell lymphomas which are morphologically and immunophenotypically similar to BL (1). In addition, gene expression signatures are highly similar to BL. At the molecular level, they exhibit chromosomal aberrations in 11q with absence of an IG::MYC rearrangement (6). This group of high-grade B-cell lymphomas previously called “Burkitt-like” lymphomas with 11q aberrations are now referred to as high-grade B-cell lymphomas with 11q aberrations (HGBL-11q). The novel terminology reflects the initial description of the entity as well as the fact that in addition to the presence of the 11q aberration and the absence of the IG::MYC juxtaposition the neoplasm may resemble non-BL like DLBCL. In particular, genetic aberrations typically observed in BL such as TCF3/ID3 mutations, are usually absent in HGBL-11q (7). Due to the fact that the cellular size can vary and cases with predominately medium- or small-cell morphology exists, the term “large B-cell lymphoma” was felt to be misleading in part of the cases by the authors of the WHO classification, though it is an alternatively accepted term. It is important to note that the term “high-grade” refers to the morphologic features and not clinical behavior (1).

The 11q aberration typically consists of a gain in 11q23.3 and a loss at 11q24.1-qter with some cases showing no 11q23.3 gain but only a telomeric loss and/or solely telomeric loss of

heterozygosity (LOH). Notably, this aberration can also occur (usually secondary) as a change in bona-fide BL, whereas MYC alterations (e.g. in the form of *MYC* gains) can also occur (secondarily) in HGBL-11q. BL and HGBL-11q share a germinal center (dark zone) gene expression profile but absence of mutations in *ID3, TCF3, SMARCA4* and CCND3 usually encountered in BL as well as presence of GNA13 mutations usually favours the diagnosis of HGBL-11q.

Diffuse large B-cell lymphomas and high-grade B-cell lymphomas

In contrast to extensive data on adult DLBCL and HGBL, molecular data on their CAYA counterparts are more limited. Clearly, the distribution in the CAYA population is skewed towards germinal center B-cell derived lymphomas as compared to the adult population (ref). Similarly, rearrangements of BCL2 and/or BCL6 seem to be less common resulting in lower frequency of DLBCL/HGBL with MYC and BCL2 rearrangements. Whereas in adults the extensive characterization of mutational profiles and gene expression signatures has been used to propose subgroups with different outcomes (8) (9) this aspect warrants further investigation in CAYA patients.

Large B-cell lymphomas

The WHO HAEM5 lists two entities of molecularly defined large B-cell lymphomas (LBCL): ALK-positive LBCL and LBCL with IRF4 rearrangement (1). Whereas the definition and outline of the ALK-positive LBCL has not been changed and requires the presence of aberrant ALK expression detected by immunohistochemistry or nucleic acid-based testing for *ALK* rearrangements or fusion transcript, the definition of LBCL with IRF4 rearrangement has been refined. IRF4 rearrangements can occur in various subtypes of B-cell neoplasms, including follicular lymphoma, DLBCL, NOS and multiple myeloma. For the diagnosis of LBCL-IRF4R, a BCL2 translocation common in (adult type) follicular lymphoma needs to be absent. Moreover, the fusion of *IRF4* to one of the three IG loci should be documented in case of an ambiguous diagnosis, as in contrast to e.g. FL or DLBCL the partner of the IRF4 locus is hardly ever (if at all) a non-IG locus in LBCL-IRF4R. Thus, the

application of an IRF4 break-apart probe might not be sufficient for the diagnosis, particular in the context of variant or even normal signal patterns. It can be helpful to document somatic hypermutation at the IRF*4* locus in this regard. Pure imbalances at the IRF4 locus in chromosome 6p25 are common in various B-cell malignancies and should not be considered as "rearrangements". Germline copy number variants of 6p25 are common and also need to be considered.

Pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma

Pediatric-type follicular lymphoma lacks the BCL2 translocation highly recurrent in (adult-type) follicular lymphoma(10) . There are morphologic and genetic overlap between the two entities however there is insufficient evidence to consider them in one umbrella entity. Notably, a recent sequencing study showed in part overlapping mutational spectra, including low genetic complexity, recurrent alterations in MAP2K1, TNFRSF14, and IRF8 and similar DNA methylation profiles (11). Nevertheless, many of the mutations detected in PNMZL were present at very low variant allele frequencies (<2%) and both morphologic subtypes still showed differences in the frequencies of the affected genes. Thus, it remains to be determined by further studies whether PNMZL and PTFL represent spectrum of a single disease of "pediatric-type follicular lymphoma with and without marginal zone differentiation" with variations in the histologic spectrum.

Primary mediastinal large B-cell and mediastinal grey zone lymphoma

Primary mediastinal large B-cell lymphoma (PMBL) and mediastinal grey zone lymphoma (MGZL) share various molecular features and are thought to derive from thymic B-cells and/or (post)-germinal center B-cells (1). Common genetic features are alterations involving 2p16 (REL), 9p24.1 (JAK2/CD274/PDCD1LG2), 16p13.13 (CIITA/C2TA), as well as changes affecting MHC expression and enhanced JAK-STAT and NFkB signaling (12). Lymphomas with features similar to MGZL presenting outside the mediastinum should be considered and diagnosed as DLBCL, NOS (13).

Biomarkers for risk stratification of common CAYA B-Cell lymphoma entities

Burkitt lymphoma (BL) and Diffuse Large B-cell Lymphoma (DLBCL) account for most cases of NHL in childhood. The current standard-of-care for BL/DLBCL with standard-risk and high-risk disease results in more than 90% 5-year event-free survival (14-16)However, the probability of survival for refractory and relapsed patients is very poor (17). Very strong prognostic parameters are absolutely necessary to identify the patients with a high relapse risk available for early clinical studies with experimental drugs. In the last decade several studies demonstrated that Minimal Disseminated Disease (MDD) at diagnosis, conducted by a long distance polymerase chain reaction (LD-PCR) assay for t(8;14)-positive patients or by qRT-PCR for patient-specific immunoglobulin (Ig) gene rearrangements, represent powerful tools for stratifying patients into different prognostic groups and monitoring treatment response (18-20). The persistence of MRD in peripheral blood after induction and consolidation therapy was also reported in a small series of children and adolescents with BL by COG (21). For patients in stage III and elevated lactate dehydrogenase (LDH), or stage IV and/or leukaemia), a recent joint EICNHL/COG randomised phase 3 trial (NCT01516580) showed that the addition of six doses of rituximab to the LMB chemotherapy backbone improved event-free and overall survival but was associated with an increase in myelotoxicity and hypogammaglobulinemia. Interestingly the AIEOP study group recently demonstrated that after the first chemotherapy course with inclusion of one dose of rituximab, the percentage of MRD-positive patients (14%, *n* = 3/21) was similar to cases receiving only chemotherapy (12%, *n* = 10/81) and the four-year PFS of MRD-negative patients demonstrated a similar trend independently of rituximab administration (22) (ritux/MRD neg:77$\pm$10%, No ritux/MRD neg: 80$\pm$5%, p<0.05). Taking into account the possible long-term effects of rituximab, rituximab should be proposed only to MRD-positive paediatric patients. On the other hand, MRD-positive patients, treated in this study with rituximab, display a better prognosis as compared to MRD-positive patients only treated with chemotherapy (ritux/MRD pos: 67$\pm$27%, No ritux/MRD pos: 50$\pm$16%; P-value<0.05) Overall, these data indicate that the analysis of MRD could also be an important tool for disease monitoring in the setting of chemo-immunotherapies; the upcoming analysis of MDD/MRD results in the Inter B-NHL ritux

2010 (NCT01516580) and B-NHL 2013 (NCT03206671) trials will definitively clarify this prognostic role.

The “MDD/MRD cells” could have peculiar features that render them resistant not only to standard chemotherapy but also to immunotherapy. Indeed, it was demonstrated in leukemia patients that MRD cells have combined properties of long-term dormancy, treatment resistance and stemness (23). Recently Polaskova and collegues analyzed three relapsed Burkitt lymphoma patients using comprehensive molecular profiling and the results underlined that tumors while exhibiting similar histological features may harbor chemotherapy-resistant, biologically and genetically distinct subclones that become more dominant after intensive chemotherapy (24), as documented by a new TP53 mutation in their case 1 at relapse. It should be of great interest to investigate if these subclones represent the MDD/MRD cells.

Noteworthy, the recent survival analysis conducted in a large pediatric cohort showed that *TP53* mutations are significantly associated with higher incidence of relapse (25 ± 4% versus 6 ± 2%, p-value 0.0002) (25). This identifies a promising molecular marker for relapse incidence in pediatric BL that could be used in future clinical trials. The analysis of the combination of these 2 prognostic parameters (MDD and TP53 mutation) in a large cohort of patients will be of utmost importance in the next future, allowing for the identification of *very high risk* and *very low risk* patients and providing a basis for a more personalized therapeutic approach able to prevent relapse. The expression of p-AKT and p-mTOR may be other potential references for diagnosis and the independent prognostic indicators of pediatric BL. Man et al(26) analyzed fifty-eight cases of pediatric BL and the results of multivariate COX proportional risk regression analysis indicated that p-AKT/p-mTOR double-positive, higher LDH and IPI score 3-5 were independent prognostic factors for both OS and PFS, and the bulky tumor (>10 cm) for PFS of pediatric BL (26). Targeting PI3K obtained some promising pre-clinical evidence, but so far lacking clinical data in BL does not allow any conclusions to be drawn.

As regards to relapses, treatment of relapsed disease should be based on a detailed molecular analysis of the most recent available sample, i.e., at the time of relapse or progression rather than on original tumor biopsy only.

In the case of DLBCL, the identification of a distinct cell-of-origin (COO) based on transcriptional signatures and the presence of specific genetic lesions has led to discovery of subtypes which carry prognostic value in adult patients (8, 27). Even though many drugs have been developed for B-cell malignancies in adults, there is wide evidence that the biology and clinical behaviour of DLBCL in children differs from that in adults (28) Therefore, specific studies need to be carried out in the paediatric population, in order to stratify patients in different risk groups, selectively target them and eradicate these neoplasms in refractory and relapsed patients.

Mature T- and NK-cell lymphomas

Mature T- and NK-cell lymphomas, non-ALCL

In children, NHL account for about 60 percent of all lymphomas in children, however mature T- and NK-cell malignancies are much rarer in the pediatric population, accounting for only about 1 percent of all pediatric NHL. This is a diverse group of disorders which can be organized into four major subtypes: leukemic, nodal, extra nodal and cutaneous. Overall, these diseases have a much higher incidence in Asian, South American, and Central American countries. In the following section, we provide a summary and recent update of the biopathologic aspects of the most common diseases and disorders in this group with respect to clinical features, immunophenotype and molecular and genetic findings. Table 1 summarizes these features in each group (1).

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

PTCL, NOS is a mature T-cell lymphoma which does not fit into any other described category. While quite rare overall, it is the most common T-cell malignancy following lymphoblastic leukaemia and anaplastic large cell lymphoma (ALCL). Typically, paediatric patients present with

mediastinal or nodal disease, however extra nodal sites including bone marrow, liver, spleen, skin and gastrointestinal tract can be involved. Patients can also present with B symptoms or paraneoplastic syndromes including eosinophilia and haemophagocytosis (29). In adult cases there are two distinct subgroups that have been found through gene expression profiling; one with high expression of GATA2 binding protein and the other with high expression of TBX21, however it is unclear if these genomics are also found in pediatric cases (30). In a described cohort of pediatric patients taken from multiple institutions on which targeted mutational analysis was done, in the patients with PTCL-NOS the most common altered gene was TET2 (specifically TET2 c.86C>G p.Pro29Arg mutation) followed by KMT2C, PIK3D, DMNT3A. Interestingly, there were not TP53 or RHOA variants found which are commonly found in adult PTCL-NOS (31). This data suggests a difference in genetic signatures between adult and pediatric cases. This is surprising due to the large number of TP53 alterations found in other pediatric tumors. Additionally, the absence of RHOA mutations combined with the low levels of PD1 expression found in this cohort suggest that pediatric PTCL-NOS has less follicular T helper cells than adult disease (31). In addition to the above gene mutations, there have also been cases showing recurrent mutations in the FYN gene as well as 9p21 loss which leads to reduced expression of CDKN2A, CDKN2B, and MTAP (30).

Angioimmunoblastic T-cell lymphoma

Angioimmunoblastic T-cell lymphoma is a lymphoma characterized by T follicular helper cells. While incredibly rare in paediatrics, there have been cases reported in the literature (30). Typical presentation is similar to adult cases which include generalized lymphadenopathy with advanced stage and spread to the liver, spleen, skin and bone marrow. Many cases are EBV-positive and have some association with chronic immunosuppression (32). Gene sequencing has shown mutations in RHOA as well as gain of function mutations in T-cell receptor related genes such as PLCG1, CD28, PIK3CA, CTNNB1, GTF21 which reflect increased activation of T-cells (32).

Extranodal NK/T cell lymphoma; nasal, extra-nasal

Patients with ENKTCL typically present with bleeding due to tumour in the nasopharyngeal or paranasal sinus area. At time of presentation, extra-nasal sites such as skin, soft tissue or GI tract can also be involved. This disease is generally localized at diagnosis, although there can be rapid dissemination to bone marrow, blood, and lymph nodes (29). There is a strong association with EBV and if tissue is not EBV-positive, diagnosis is ruled out (32). Chromosomal abnormalities such as 6q deletion, rearrangement of chromosome X (Xp21-ter), translocations with chromosome 8, FAS mutations, and JAK/STAT signalling pathway alterations have been found (32). Recently, there have been studies done which suggest that the HLA-DPB1 gene leads to potential susceptibility of ENKTCL(33). Data from the EICNHL and I-BFM groups show a 5 year overall survival of 59 percent (34).

Hepatosplenic T-cell lymphoma

Hepatosplenic T-cell lymphoma (HSTCL) is an aggressive malignancy which arises from cytotoxic T-cells, typically γδ T-cells. The peak age of onset is adolescence and there is a male predominance. Typical presentation is hepatosplenomegaly, systemic symptoms, cytopenias, lack of lymphadenopathy and bone marrow involvement with high stage at presentation. There is a strong association between HSTCL and patients who have underlying chronic immune suppression or immunodeficiencies, particularly those with Chron's disease (29). There are well documented cytogenic abnormalities in HSTCL which include isochromosome 7q along with trisomy 8 and loss of sex chromosomes (30). These chromosomal abnormalities typically lead to gene expression imbalances in IKZF1 and PTPN12, which are genes responsible for regulation of immune cell development and tumor suppressor genes respectively (32). In a multi-institutional cohort of patients on which targeted mutational analysis was done, there were 4 patients with HSTCL included. It was found that the majority (3 of the 4 patients) had TET2, KMT2C, SETD2, STAT5B, and FLT3 variants. Interestingly, in this same cohort, none of the patients had mutations in DNMT3A, PIK3CD, STAT3, or TP53 which are found in adult cases of HSTCL (31). Overall, prognosis of this disease remains rather poor, with data from the EICNHL and I-BFM groups

showing a 5 year overall survival rate of 13 percent, leading to continued discussion regarding optimal treatment for these patients (34).

Subcutaneous panniculitis-like T-cell lymphoma

Subcutaneous panniculitis like T-cell lymphoma (SPCTL) is a lymphoma of mature cytotoxic TCRαβ -cells. The typical presentation is that of subcutaneous plaques or nodules which generally affect the trunk and extremities. Cytopenia is also common at presentation, and there are rare reports of bone marrow involvement, however in about 20 percent of cases patients present with hemophagocytic lymphohistiocytosis which is associated with a worse clinical course (35). There are recurrent chromosomal abnormalities in 1qter, 2qter, 11qter, 12qter, 17p, 19, 20 and 22 which can be seen in other T-cell malignancies as well as gain of chromosomes 5q and 13q which are unique to SPTCL (36). Recent data has suggested HAVCR2 germline mutations as a genetic factor that predisposes to SPTCL in adults, however in a paediatric cohort of cases which were analysed, both of the two SPTCL cases had wild type HAVCR2 status (31). 5 year overall survival is about 78 %(34). An unusual neoplasm with clinical and pathological features of SPCTL with gamma/delta immunophenotype was shown to harbor biallelic HAVCR2 germline mutations (37).

Primary cutaneous gamma delta T-cell lymphoma

Primary cutaneous gamma delta T-cell lymphoma (PCGDTCL) was previously classified with SPTCL but since the 2008 revision of the WHO classification it is now a separate entity, largely in part because of the prevalence of the expression of γδ T-cells rather than the classically seen αβT cells of SPTCL as well as the overall worse prognosis (38). While it mostly occurs in adults, there have been paediatric cases reported (39). Patients usually present with cutaneous lesions that on histology appear similar to SPTCL, however with involvement of the epidermis and dermis. PCGDTCL is clinically more aggressive than SPTCL with a much worse prognosis overall.

Mycosis fungoides

Mycosis fungoides is a cutaneous T-cell lymphoma which typically presents with a widespread rash in both sun exposed and non-sun exposed areas. In children, the lesions are more frequently hypopigmented in over half of the cases (40). Due to the appearance at presentation, MF is often misdiagnosed with the differential including psoriasis, systemic lupus erythematosus, and chronic or atopic dermatitis. The majority of paediatric cases being CD8 positive, compared with adult cases which are usually CD4 positive. There are no specific cytogenic abnormalities which have been found, however greater than 75% of cases will have clonal *T cell receptor* gene rearrangements (29).

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma

This is an extremely rare variant of cutaneous T-cell lymphomas which has very limited case reports in the paediatric age range. Overall, patients typically present with widespread disease of the skin (plaques and tumours with haemorrhagic ulcers and necrosis) and spread to other extracutaneous sites is not uncommon, resulting in a poor prognosis. Recently, Bastidas Torres et all performed a study using whole genome and RNA sequencing techniques to describe genetic alterations in this entity. They found recurrent gains within 7q and 17q as well as losses within 1p and 13q. There was also a large predominance of JAK-STAT pathway gene alterations (41).

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

This disorder was previously termed primary cutaneous CD4+ small/medium T-cell lymphoma, however the classification was modified in the 2017 WHO classification updates due to the uncertainty surrounding its malignant potential as well as the overall indolent course of the disorder (42). Patients typically present with a solitary nodule or papule on the head, neck or upper extremities, although 25 percent of cases present as multiple lesions. While rare, there have been pediatric cases reported. Overall, there is an excellent prognosis of this disorder.

Hydroa vacciniforme-like T-cell lymphoma

Hydroa vacciniforme-like T-cell lymphoma is an EBV-associated cutaneous T-cell lymphoma with clinical features including edema, blisters, ulcers, and scars on sun exposed areas mainly on the face and upper extremities (43). Patients can also present with systemic symptoms including fever, weight loss, hepatosplenomegaly, and lymphadenopathy. Etiology is thought to be from transformation of EBV-infected cells with high viral loads being associated with a poor prognosis (43). Biopsy shows angiocentric features with infiltration of atypical cells throughout the dermis and subcutis. Cells are typically positive for CD3, CD45, CD56, and *TCRγ* rearrangement (29).

Chronic lymphoproliferative disorder of T/NK-cells or chronic active EBV (CAEBV) disease

CAEBV is a disorder in which patients who become infected with EBV or reactivate a prior EBV infection develop a disease which does not resolve. Patients typically present with a chronic course of intermittent symptoms such as fever, EBV hepatitis, persistent lymphadenopathy, splenomegaly. Because they are unable to control the EBV infection, they begin to have tissue infiltration from EBV positive T- or NK-cells (very rarely B-cells) (44). This disease predominantly occurs in East Asia and Latin American regions. In patients with this disease, there have been whole exome sequencing analyses done showing that germline mutations are rare, however there are some somatic mutations such as DDX3X that are frequently found in the infected cells which are associated with hematologic malignancies which suggests that these mutations that are acquired in infected NK- or T-cells can result in transformation to NK- or T-cell lymphomas (44).

Systemic EBV-positive T-cell lymphoma of childhood

In the 2017 WHO classification update, systemic EBV-positive lymphoproliferative disease of childhood was renamed as systemic EBV-positive T-cell lymphoma of childhood due to its aggressive nature (45). Systemic EBV-positive T-cell lymphoma of childhood is a clonal and clinically aggressive proliferation of EBV-infected cytotoxic T-cells. The typical presentation of this disease is an acute onset of symptoms with patients presenting with lymphadenopathy, fever, splenomegaly, hepatomegaly, cytopenia and often hemophagocytic lymphohistiocytosis after an

acute EBV infection or reactivation of a prior infection. The affected T-cells, which are usually αβ T-cells phenotypically, are most often EBV IgM negative and IgG positive with EBER positivity (32). Clinically, the disease usually takes a fulminant course with survival being not long after diagnosis.

Anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) ALK+ is the most prevalent form of peripheral T cell lymphoma diagnosed in the CAYA population (1). The large majority of cases are defined by expression of the t(2;5)(p23;q35) breakpoint product Nucleophosmin 1-Anaplastic Lymphoma Kinase (NPM-ALK) as well as expression of CD30, and usually a T-cell marker such as CD4 (46). For the most part, children are treated with the ALCL99 therapeutic protocol which leads to good survival outcomes although relapse is not uncommon, but tumours tend to remain chemosensitive (47, 48). However, ALCL99 therapy is not without its toxicities and efforts to understand the biology underlying this disease have led to improved treatment options.

Biomarkers for treatment stratification

One way to reduce the toxicity of the ALCL99 backbone chemotherapy would be to identify low risk children towards administration of a reduced chemotherapeutic burden. For example, some children produce an immune response to aberrantly expressed ALK protein that can be monitored by the detection of circulating ALK autoantibodies – children with higher titres of these antibodies have a better prognosis particularly when they also lack disseminated disease(49). In the latter regard, minimal disseminated disease (MDD) can be detected in peripheral blood and bone marrow samples by qualitative and quantitative PCR-based methodologies. Most recently, digital droplet PCR has shown consistency across inter-lab quality control and shows the most promise as a clinically applicable biomarker – this remains to be prospectively validated in a trial setting as does the detection of circulating ALK autoantibodies which to date has proven difficult to standardise (50). This is largely due to the subjective nature of the established ALK autoantibody

assay which utilises an ELISA-based approach of ALK-expressing cells (cos cells transfected to express ALK) adhered to glass slides as cytospins. Improvements in the technology to detect ALK autoantibodies have so far proven to be unsuccessful or cannot replicate the results of retrospectively conducted studies. Regardless, biomarkers are only applicable to children receiving the same treatment regimen as those that were studied to develop said biomarkers. With the advent of novel treatment approaches, these will have to be re-assessed for their prognostic relevance particularly as ALK tyrosine kinase inhibitors (TKI) are introduced into upfront treatment regimens (48).

Novel treatment approaches

Given that ALCL is largely driven by aberrant ALK expression, it naturally follows that ALK TKI are a rational treatment approach. Unfortunately, interest in the development of ALK TKIs did not peak until expression of ALK in an adult cancer was reported in 2007, i.e., non-small cell lung cancer, some years after the cloning of NPM-ALK from ALCL in 1984 (46, 51). Now there are 1st, 2nd and 3rd generation inhibitors although not all are available to, nor approved for use in children (48, 52). Most clinical experience of ALK TKIs in the treatment of ALCL, until recently, came from compassionate use before trials were initiated for relapse/refractory disease and then for upfront treatment (53). Results of these trials have thrown up some perhaps unexpected and interesting insights that have confirmed the need for specific paediatric trials of these agents. For example, the ITCC CRISP trial of the ALK TKI crizotinib combined with vinblastine for r/r ALCL proved to be toxic resulting in a patient death due to neutropenia and infection and led to an early close to this arm of the trial. Similar toxicities were independently noted in a German study whereby this treatment regimen had to be discontinued, paused or reduced due to toxicities (54). Furthermore, addition of crizotinib to the ALCL99 backbone in the COG ANHL12P1 trial (NCT01979536) (55) was temporarily paused due to a number of patients developing thromboembolisms and another trial reported unacceptable cytopenias and gastrointestinal toxicity (56). None of the ALK TKI seem to be without some form of treatment-limiting side-effect whether that be ocular disturbances as noted in children treated with crizotinib, to weight gain and psychological effects in those treated with lorlatinib (57). As such, ALK TKIs are far from being magic bullets not least due to rapid

relapses observed on cessation of therapy. This latter aspect is of significant concern as we risk producing a generation of ALCL survivors on long-term ALK TKI therapy with unknown future health consequences. What is clear is that ALK TKI alone are not sufficient, yet addition to other, perhaps well-known and used standard chemotherapeutic agents can lead to unexpected toxicities.

This leaves us with a clinical conundrum and perhaps an ethical dilemma – continue with a successful, well-established, yet toxic backbone (ALCL99), or introduce new agents that may create a chronic condition with unknown, long-term consequences (58). This issue may, in part, be overcome by the implementation of metronomic dosing or using drug holidays. When combined with assessment of minimal residual disease (MRD) using PCR techniques as outlined above, this approach has been shown in a few cases to be successful (59, 60). Indeed, biological studies have shown that this approach increases the time it takes for resistance to ALK TKI to develop (61). However, knowing when to cease treatment with ALK TKI is another clinical issue for which there is no answer at present, particularly as rapid relapses have been noted on cessation of therapy(62). However, patients that relapse tend to remain chemosensitive with those that develop resistance doing so very early during treatment. It is also therefore important that mechanisms of resistance to ALK TKI are investigated and this has been the subject of much research activity whereby not only mutations in the target protein ALK have been detected, but also amplifications (53). Another mechanism of resistance is the activation of ALK bypass pathways which to date have largely been elucidated through *in vitro* CRISPR screens with validation in limited numbers of patient samples (63-65). In time, and with more experience in the use of ALK TKIs in a paediatric population, it should be possible to prevent the development of resistance by upfront treatment with combinations of agents. Finding the answers requires us to significantly improve our understanding of the biology of this malignancy particularly at the sub-clonal level.

Hopes for new therapeutic approaches gleaned from knowledge of ALCL biology

Improved understanding of the signalling pathways emanating from aberrant ALK activity has provided novel targets for therapy. However, many of these are some ways from clinical application as they are pre-clinical compounds. One example is the newly developed METTL3 inhibitor, a novel class of drug that inhibits RNA modification enzymes which has been shown to act in synergy with ALK TKI and furthermore to alter the mode of cell death induced by the latter from a senescence-like growth arrest to apoptosis (65). Others exploit the immune system which is clearly active in ALCL as evidenced by both cellular and humoral responses to ALK (66-69) although ALCL cells are known to evade the immune system by a number of mechanisms including down-regulation of CD48 (68) and expression of PD-L(70). Indeed, a trial applying nivolumab to the treatment of r/r ALCL is underway (NCT03703050)(48). In summary, there are many potential therapeutic options for children with ALCL, many gleaned from understanding the biology of this disease, but choosing the most promising for implementation in clinical trials is not an easy task particularly given the relative rarity of this malignancy.

Summary

Mature NHLs in the CAYA population are rare and exhibit unique clinical, immunophenotypic and genetic characteristics. Application of large-scale unbiased genomic and proteomic technologies such as gene expression profiling and next generation sequencing (NGS) have led to enhanced understanding of the biopathologic features for many lymphomas. These insights have provided opportunities to gain novel insights regarding targeted therapies and disease-specific monitoring using circulating biomarkers. Recent studies demonstrate that genetic alterations in lymphomas of CAYA are distinct from those of the adult population (25). Investigations into the use of MRD/MDD using a variety of molecular methods for patients with B- and T-cell lymphomas have demonstrated promising results which will provide opportunities for risk stratification to minimize toxicity.

Acknowledgements:

RS received funding from Deutsche Forschungsgemeinschaft through SFB 1074 (Project B9), European Union (Next Level: On the road to excellence in unravelling the (epi)genetic landscape of hematologic neoplasms; Grant agreement No 952304).

ST received funding from Cancer Research UK Cambridge Centre [CTRQQR-2021\100012].

Conflict of interest statement:

All authors declare no conflict of interest.

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Table 1. Overview of pediatric mature T cell lymphomas (excluding ALCL)

Disease	Proportion	Phenotype	EBV status	Genetics
Peripheral T cell lymphoma, NOS	30-50%	CD3+, CD4+, TCR ß CD2-, CD5-, CD7-, CD8-	Usually negative	Mutations in TET2, KMT2C, PIK3D, DMNT3A, FYN gene, 9p21 loss
Angioimmunoblastic T cell lymphoma	3%	CD4+, BCL6+, CXCL13+, PD1+	Usually positive	RHOA, PLCG1, CD28, PIK3CA, CTNNB1, GTF21
Extranodal NK/T cell lymphoma	5%	CD2+, CD3+, CD56+, TIA-1+, Granzyme B+, EBER+	Usually positive	Loss of 6q21-25, isochromosome 6p, chromosome 8 translocation, FAS mutations, JAK/STAT signalling pathway alterations, germline mutations of HLA-DPB1 gene
Hepatosplenic T cell lymphoma	5-14%	CD3+, CD56+, TIA-1+, TCRγ+, CD4-, CD5-, TCRβ-, perforin-, granzyme-	Negative	Isochromosome 7q, trisomy 8, loss of Y, mutations in TET2, KMT2C, SETD2, STAT5B, and FLT3
Subcutaneous panniculitis-like T-cell lymphoma	1-12%	CD3+, CD8+, TCRβ+, TIA-1+, Granzyme+, CD4-, CD5-, CD56-, TCRγ-	Negative	Gain of 5q,, 13q and loss of 1q, 2q,11q, 12q, 17p, 19, 20, 22, mutations in HAVCR2
Mycosis fungoides	5%	CD8+>CD4+	Negative	Unknown
Primary cutaneous gamma delta T cell lymphoma	16%	CD3+, CD56+, TCRγ+, CD4-, CD8-, CD5-, TCRβ-	Negative	Unknown
Primary cutaneous CD8+ aggressive cytotoxic T-cell lymphoma	Unknown	CD3+, CD8+, Granzyme B+, TIA-1+, CD4-, CD56-, EBER-, CD30-	Negative	7q and 17q gains, 1p and 13q loss, JAK-STAT pathway alterations
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma	Unknown	CD3+, CD4+, PD-1+, CXCL13+, BCL-6+,	Negative	Unknown
Hydroa vacciniforme-like lymphoma	1-21%	CD3+, TCRγ+, EBER+, CD4-, CD8-	Positive	Unknown

Systemic EBV-positive lymphoproliferative disease	5%	CD3+, CD8+ (sometimes CD4+), Perforin+, Granzyme B+, TIA-1+, EBER+, CD56-	Positive	Unknown

Practice Points

- Non-Hodgkin lymphomas of CAYA represent a heterogeneous group of rare neoplasms.
- Rare subtypes of childhood B-cell lymphomas such as pediatric-type follicular lymphoma and large B-cell lymphoma with IRF4 rearrangement exhibit unique clinical and pathologic features.
- MRD/MDD has demonstrated prognostic significance for mature B-cell lymphomas and ALK+ ALCL.

Research Agenda

There are numerous opportunities related to future research in the study of biopathological aspects of NHL in CAYA. The cell-of-origin or normal cellular counterparts for most NHL of the CAYA population is unknown. Mutational profiles and gene expression signatures that may provide insights regarding prognostically relevant subgroups of DLBCL have not been developed or evaluated in the CAYA population and warrants further investigation in CAYA patients. The biopathologic and genetic features of most non-ALCL mature T cell lymphomas need to be characterized. The impact of immune deficiency/dysregulation such as inborn errors of immunity (IEI) on lymphoproliferations in CAYA is largely unexplored. The impact of germline genetic testing in conjunction with tumor NGS analysis will be important to learn more about the role of genetic tumor syndromes associated with lymphomagenesis. Given the challenges with obtaining sufficient primary tissue biospecimens in this disease group, the clinical utility of evaluating blood-based biomarkers such as circulating tumor DNA and/or cell-free DNA for disease monitoring represents a critical opportunity for future research.