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Diagnosis and management of rare paediatric Non-Hodgkin lymphoma

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ABSTRACT

Mature B-cell lymphomas, (B- or T-cell) lymphoblastic lymphomas (LBL), and anaplastic large cell lymphoma (ALCL) correspond to about 90% of all non-Hodgkin lymphoma (NHL) cases occurring in children and adolescents. The remaining 10% encompass a complex group of entities characterized by low/very low incidences, paucity of knowledge in terms of underlying biology in comparison to their adult counterparts, and consequent lack of standardization of care, information on clinical therapeutic efficacy and long-term survival. At the Seventh International Symposium on Childhood, Adolescent and Young Adult NHL, organized on October 20–23, 2022, in New York City, New York, US, we had the opportunity to discuss clinical, pathogenetic, diagnostic, and treatment aspects of certain subtypes of rare B- or T-cell NHL and they will be the topic of this review.

1. Introduction

Non-Hodgkin lymphoma (NHL) represents the third most common cancer in children and adolescents <19 years of age [1]. Although the term "rare NHL" is not clearly defined regarding the incidence, primary site of involvement or the denominator referred to, it is usually used for all subtypes not being Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), (precursor B- and T-cell) lymphoblastic lymphoma (LBL), and anaplastic large cell lymphoma (ALCL) [2–4]. While they account for 90% of all cases, the remaining are uncommon histologies of B-, T-, or NK (natural killer)-cell lineages [2]. Due to the rarity of such NHL in childhood and adolescence, prospective biological and therapy studies have posed significant hurdles and are therefore lacking.

The present review summarizes the clinical, histopathological and molecular features as well as the treatment and outcome of selected rare mature NHL subtypes in children and adolescents. Our focus will be certain *[i]* B-cell entities, such as paediatric-type follicular lymphoma (PTFL), marginal zone lymphoma (MZL), and large B-cell lymphoma (LBCL) with *IRF4*-rearrangment (LBCL-IRF4), and *[ii]* T/NK-cell entities, such as rare forms of mature (non-cutaneous) peripheral T-cell lymphoma (PTCL), and Epstein-Barr virus (EBV)-positive NK/T-cell lymphomas, such as extra-nodal NK-cell lymphoma (ENKL).

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List of abbreviations

ALCL	anaplastic large cell lymphoma
BCL	B-cell lymphoma
BL	Burkitt lymphoma
BM	bone marrow
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CNS	central nervous system
COG	Children's Oncology Group
CSF	cerebrospinal fluid
DLBCL	diffuse large B-cell lymphoma
EBER-ISH	EBV-encoded small RNA *in situ* hybridization
EICNHL	European Intergroup for Childhood NHL
ENKL	extra-nodal NK-cell lymphoma
ENKTL	extra-nodal NK/T-cell lymphoma
EMZL	extranodal marginal zone lymphoma
EFS	event-free survival
FISH	fluorescence *in-situ* hybridization
FL	follicular lymphoma
GC	germinal centre
i-BFM	international Berlin-Frankfurt-Münster
IG	immunoglobulin
IPNHLSS	International Paediatric NHL Staging System
LBL	lymphoblastic lymphoma
LCBL	large B-cell lymphoma
LBCL-IRF4	large B-cell lymphoma with *IRF4*-rearrangment
LDH	lactate dehydrogenase
LN	lymph nodes
MALT	mucosa-associated lymphoid tissue
MDR	Multi-Drug Resistance
MZL	marginal zone lymphoma (MZL)
NHL	non-Hodgkin lymphoma
NK	natural killer
NMZL	nodal marginal zone lymphoma
OS	overall survival
PCR	polymerase chain reaction
PD-L1	programmed death protein ligand 1
P-gp	P-glycoprotein
PNMZL	paediatric nodal marginal zone lymphoma
PTCL	peripheral T-cell lymphoma
PTFL	paediatric-type follicular lymphoma
R	rituximab
R–CVP	R-cyclophosphamide, vinblastine/vincristine, prednisone
R–COP	R-cyclophosphamide, vincristine, prednisone
r/r	relapsed/refractory
RT	radiation therapy
SCT	stem cell transplantation
TFH	T-follicular helper
TCL	T-cell lymphoma
WHO	World Health Organization
WHO-HAEM5	The 5th Edition of the World Health Organization Classification of Haematopoietic and Lymphoid Tissues

2. Mature B-cell neoplasms

2.1. Paediatric-type follicular lymphoma

Paediatric-type follicular lymphoma (PTFL) is a nodal mature B-cell lymphoma (BCL) that occurs primarily in the paediatric and adolescent age, but also sporadically affects young adults and older individuals. It is included as a distinct entity in the 5th *Edition of the*

Tables 1
Non-Hodgkin lymphoma according to the World Health Organization, 2022 [5][a].

B-CELL LYMPHOMAS
Precursor B-cell lymphomas
B-cell lymphoblastic lymphoma
- B-lymphoblastic lymphoma, not otherwise specified
- B-lymphoblastic lymphoma with defined genetic abnormalities[b]
- B-lymphoblastic lymphoma with defined genetic abnormalities

Mature B-cell lymphomas
Pre-neoplastic and neoplastic small lymphocytic proliferations
- Small lymphocytic lymphoma

Splenic B-cell lymphomas
- Splenic marginal zone lymphoma
- Splenic diffuse red pulp small B-cell lymphoma
- Splenic B-cell lymphoma

Lymphoplasmacytic
- Lymphoplasmacytic lymphoma

Marginal zone lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
- Primary cutaneous marginal zone lymphoma
- Nodal marginal zone lymphoma
- Paediatric marginal zone lymphoma

Follicular lymphoma
- *In situ* follicular B-cell neoplasm
- Follicular lymphoma
- Paediatric-type follicular lymphoma
- Duodenal-type follicular lymphoma

Cutaneous follicle centre
- Primary cutaneous follicle centre lymphoma

Mantle cell lymphoma
- *In situ* mantle cell neoplasm
- Mantle cell lymphoma
- Leukaemia non-nodal mantle cell lymphoma

Transformation of indolent B-cell lymphomas
Large B-cell lymphomas
- Diffuse large B-cell lymphoma, not otherwise specified
- T-cell/histiocyte-rich large B-cell lymphoma
- Diffuse large B-cell lymphoma/high grade B-cell lymphoma with *MYC* and *BCL2* rearrangements
- ALK-positive large B-cell lymphoma
- Large B-cell lymphoma with *IRF4* rearrangement
- High-grade B-cell lymphoma with 11q aberrations
- Lymphomatoid granulomatosis
- EBV-positive diffuse large B-cell lymphoma
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Fibrin-associated large B-cell lymphoma
- Fluid overload-associated B-cell lymphoma
- Plasmablastic lymphoma
- Primary large B-cell lymphoma of immune-privileged sites
- Primary cutaneous diffuse large B-cell lymphoma, leg-type
- Intravascular large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma

Large B-cell lymphomas, continuation
- Mediastinal grey zone lymphoma
- High-grade B-cell lymphoma, not otherwise specified

Burkitt lymphoma
KSHV/HHV8-associated B-cell lymphoid lymphomas
- Primary effusion lymphoma
- KSHV/HHV8-positive diffuse large B-cell lymphoma

T- AND NK-CELL LYMPHOMAS
Precursor T-cell lymphomas
- T-lymphoblastic lymphoma, not otherwise specified
- Early T-precursor lymphoblastic lymphoma

Mature T-cell and NK-cell lymphomas
- Adult T-cell leukaemia/lymphoma
- Sezary syndrome

Primary cutaneous T-cell lymphomas

(*continued on next page*)

Tables 1 (*continued*)

- Mycosis fungoides
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: lymphomatoid papulosis
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous gamma/delta T-cell lymphoma
- Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous peripheral T-cell lymphoma, not otherwise specified
- Intestinal T-cell and NK-cell lymphomas
- Indolent T-cell lymphoma of the gastrointestinal tract
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Intestinal T-cell lymphoma, not otherwise specified

Hepatosplenic T-cell lymphoma

Anaplastic large cell lymphoma

- ALK-positive anaplastic large cell lymphoma
- ALK-negative anaplastic large cell lymphoma
- Breast implant-associated anaplastic large cell lymphoma

Nodal T-follicular helper (TFH) cell lymphoma

- Nodal TFH cell lymphoma, angioimmunoblastic-type
- Nodal TFH cell lymphoma, follicular-type
- Nodal TFH cell lymphoma, not otherwise specified

Other peripheral T-cell lymphomas

- Peripheral T-cell lymphoma, not otherwise specified

EBV-positive NK/T-cell lymphomas

- EBV-positive nodal T- and NK-cell lymphoma
- Extranodal NK/T-cell lymphoma

EBV-positive T- and NK- lymphomas of childhood

- Systemic EBV-positive T-cell lymphoma of childhood

[a] "*KSHV/HHV8*-associated B-cell lymphoid proliferations", "lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation", "tumour-like lesions with T-cell predominance", "intestinal T-cell and NK-cell lymphoid proliferations" and "EBV-positive T- and NK-cell lymphoid proliferations" are not listed in this table.

[b] Defined genetic abnormalities include: B-lymphoblastic lymphoma with [*i*] hyperdiploidy, [*ii*] with hypodiploidy, [*iii*] with iAMP21, [*iv*] with *BCR::ABL1* fusion, [*v*] with *BCR::ABL1*-like features, [*vi*] with *KMT2A* rearrangement, [*vii*] *ETV6::RUNX1* fusion, [*viii*] with *ETV6::RUNX1*-like features, [*ix*] with *TCF3::PBX1* fusion, [*x*] with *IGH::IL3* fusion and [*xii*] *TCF3::HLF* fusion.

World Health Organization (WHO) Classification of Haematopoietic and Lymphoid Tissues (WHO-HAEM5) (Table 1) [5], and accounts for <2% of childhood NHL [6–12]. Paediatric-type follicular lymphoma is characterized by a clonal proliferation of germinal-centre (GC) B-cells with a pure follicular growth pattern and a high proliferation index [5]. Extra-nodal cases, such as testicular follicular lymphoma (FL), are considered unrelated lesions and are morphologically distinct [5]. Cases with diffuse areas indicating DLBCL, LBCL-IRF4, and cases with *IG*-, *BCL2*-, or *BCL6*-translocations are excluded by definition (Table 2) [5]. Importantly, most reports published to date on PTFL have not used the updated definition of the WHO-HAEM5 [5].

2.1.1. Clinical and diagnostic characteristics

Most cases of PTFL involve the lymph nodes (LN) of the head and neck region, present with stage I/II disease, have a Karnofsky index of 90–100%, and lack B-symptoms [6,11,13–15]. However, in order to establish comprehensive data for this ultra-rare disease and deduce therapy recommendations, two of the largest consortia in childhood NHL, the European Intergroup for Childhood NHL (EICNHL) and the international Berlin-Frankfurt-Münster (i-BFM) Group, performed a retrospective multinational study addressing the clinical features and outcome of 63 paediatric FL patients [14]. This study demonstrated that paediatric FL is usually associated with male sex, adolescent age, low serum lactate dehydrogenase (LDH) levels and localized (I/II) stage disease, mostly involving the peripheral LN [14]. As this study also identified cases of advanced (III/IV) stage disease, authors concluded that the initial diagnostic work-up should still follow the Revised International Paediatric NHL Staging System (IPNHLSS) [14,16]. Clinical observations of cases with histologically and genetically typical PTFL, but stage III disease (*i.e.*, mediastinal tumour), might question the necessity to really include disease stage in the definition of PTFL. Whether analysis of the bone marrow (BM) and central nervous system (CNS) is needed in PTFL is a matter of debate but might be waived. Due to its rarity, only a few case reports and series on PTFL had been published until the EICNHL/i-BFM study, with patient numbers ranging from 4 to 25 and including patients with testicular FL or advanced-stage disease of whom none would have been classified as PTFL according to WHO-HAEM5 (Table 2) [5,6,11,13,17–22]. Nevertheless, they showed similar clinical and outcome findings as in the EICNHL/i-BFM study [5,6,11,13,17–22].

Large B-cell lymphoma-IRF4 as the most important differential diagnosis (Table 2) usually involves the Waldeyer's ring (palatine, tonsils) or LN in the head and neck region or, occasionally, the gastrointestinal tract [23–27]. Moreover, it seems to be associated with

Table 2
Differential diagnosis of pediatric-type follicular lymphoma, large B-cell lymphoma with *IRF4* rearrangement and paediatric nodal marginal zone lymphoma.

Diagnostic criteria	Pediatric-type follicular lymphoma	Large B-cell lymphoma with *IRF4* rearrangement	Paediatric nodal marginal zone lymphoma
Gender	male predominance	male predominance	male predominance
Median age	≥10–15 years	≥10 years	≥10–15 years
Effaced architecture	at least partially effaced[a] „Node in node" feature +/-	at least partly effaced[a]	at least partly effaced[a]
Follicular architecture	pure[a]	pure follicular or follicular and diffuse[a]	follicular colonization interfollicular proliferation and marginal zone expansion[a]
Diffuse areas of large cells	absent[a]	often	often
Zonation of germinal centres	absent or blurred	absent	residual follicles with PTGC-like features
Starry sky pattern	present	absent	often
Cytology in follicles	monotonous medium sized cells, atypical centrocytes and centroblasts large nucleoli rare	monotonous large cells with variable cytology mostly centroblasts large nucleoli	disrupted follicular DC meshwork; mantle cells extending to GC, resembling PTGC small to medium sized with monocytoid and centrocyte-like cells
Localization	mostly lymph nodes in the head and neck region[a] (localized stage[a])	tonsils ± lymph nodes in the head and neck region[a] gastrointestinal tract (mostly localized stage)	mostly lymph nodes in the head and neck region[a] (mostly localized stage)
Immunophenotype	CD20^{+}[a], BCL6+[a], CD10+/(-), BCL2-/+, MUM1-/+	CD20^{+}[a], BCL6+[a], CD10-/+, BCL2+/-, MUM1++[a]	BCL2+[a], CD43^{+}[a], CD20^{+}, BCL6-, CD10-/+, PD1+ cells in reactive GC
Clonal *IGH/IGK* r.	+[b]	+	+[b,a]
Translocations: *BCL2, BCL6, IG, MYC, IRF4*	absent[a]	*IRF4:* present[a,c] *IGH*+, *BCL6* -/+ *BCL2*, *MYC*: absent[a]	absent[a] *IGH* + cases reported

Abbreviations: GC, germinal centres; DC, dendritic cells, r., rearrangements; PTGC, progressive transformation of germinal centres.
[a] Essential diagnostic criteria.
[b] Prove of clonality is strongly recommended.
[c] Exceptional otherwise highly typical cases without proven *IRF4*-rearrangement might be accepted.

male sex, school-age at diagnosis, normal LDH values, lack of B-symptoms, and mostly localized disease [23].

2.1.2. Histopathology and molecular features

The diagnosis of PTFL is challenging because it closely resembles LN with marked reactive follicular hyperplasia. Regarding macroscopic appearance, involved LN present as enlarged and encapsulated nodes without sclerosis or necrosis. Lymph node architecture is at least partly effaced by atypical, enlarged, and sometimes floral, serpiginous, or confluent follicles. Mantle zones are thinned or absent. Germinal centres are expansile and lack zonation, but might contain tingible-body macrophages. A typical feature of PTFL is the persistence of a thin peripheral area of uninvolved lymphoid tissue with preserved smaller reactive follicles, referred to as a "node-in-node" pattern. Almost all PTFLs would be defined as a grade 3b FL as they are almost exclusively composed of "blasts" with few, if any, centrocytes. As this grading has no implication in PTFL, it is usually not reported, which is in line with the updated definition of WHO-HAEM5 [5]. Any diffuse area of large cells consistent with DLBCL excludes PTFL.

Paediatric-type FL usually consists of blastoid cells (resembling cells intermediate between centrocytes and centroblasts) with small nucleoli. The neoplastic cells are always positive for the B-cell markers CD20, CD79a, and PAX5 as well as BCL6. Most cases also express CD10, while BCL2 is usually negative. The proliferation index is high (>30%). In immunohistochemically BCL2-positive cases, it is mandatory to exclude the presence of a *BCL2*-rearrangement by fluorescence *in-situ* hybridization (FISH), as the very rare paediatric *BCL2*-rearranged FL should be classified as an adult-type FL. Expression of IRF4/MUM1 is usually negative or stains only sparse cells with plasmocytic differentiation.

A monoclonal *IGH* and/or *IGK* gene rearrangement can be detected in nearly all PTFL cases and allows to differentiate it from florid reactive follicular hyperplasia. Exclusion of translocations of *BCL2*, *IRF4*, *IG*, and *BCL6* genes by FISH is a mandatory diagnostic criterion [5]. Recurrent aberrations in PTFL are deletions at 1p36 (including *TNFRSF14*) and mutations *of TNFRSF14*, *MAP2K1*, and *IRF8* [28].

Large B-cell lymphoma-IRF4 as the most important histological differential diagnosis may have different patterns of growth which are diffuse, follicular and diffuse, or purely follicular, with the latter closely resembling PTFL (Table 2) [5,23]. The neoplastic follicles of LBCL-IRF4 are large and round and lack the serpiginous configuration of PTFL. Morphologically, it is a high-grade neoplasm showing either sheets of typical centroblasts or more frequently monotonous medium-sized blastoid cells with small nucleoli. However, unlike PTFL, a "starry sky" pattern is usually absent. The neoplastic cells are usually positive for the B-cell markers CD20, CD79a, and PAX5. BCL6 and CD10 are invariably positive. The main immunophenotypic feature is the strong expression of IRF4/MUM1 and concomitant absence of PRDM1/BLIMP1. Large B-cell lymphoma-IRF4 shows a high proliferation index and rearrangements of immunoglobulin (*IG*) cluster. The main molecular marker is a genetically cryptic rearrangement of *IRF4* with an *IGH* locus. However, rare cases for which the *IRF4*-translocation cannot be documented, are still accepted if clinical presentation and immunohistochemistry are in line with the WHO-HAEM5 [5]. *BCL2* and *C-MYC* are never rearranged, whereas in a subset aberrations affecting *BCL6*

are detected. Somatic *BCL6* mutations are frequent, as are mutations in *IRF4* and NF-kB pathway genes (*CARD11*, *CD79b*, and *MYD88*) [26,29].

2.1.3. Therapy and outcomes

In contrast to adult-type FL, which is usually of low-grade morphology and an incurable disease despite variable treatment approaches, prognosis of PTFL is extremely good after less-intense chemotherapy or complete resection followed by watchful waiting. Survival rates exceed 95% [11,13,14,17–21,30]. According to the EICNHL/i-BFM study, 44/63 FL patients (70%) received polychemotherapy and one (2%) rituximab (R) only, while 17 (26%) followed a watch-and-wait strategy (all with upfront complete resection) [14]. In one patient (2%) the type of therapy was not reported. Of the 39/44 patients with available information, all but three patients received low- or intermediate-risk B-NHL-derived therapy. Only one/63 patients (2%) relapsed (after watchful waiting) and none of the patients died from the lymphoma itself or therapy-related toxicity. The 2-year event-free survival (EFS) and overall survival (OS) rates were 94% ± 5% and 100%, respectively, after a median follow-up of 2.2 years [14]. Of the 32 patients with initial complete resection (including 30/36 stage I patients), 17 (53%) children had no additional therapy with only one local relapse, indicating no systemic disease in localized PTFL. The excellent overall outcome of the EICNHL/i-BFM cohort of 63 FL patients is comparable to the results available in the literature, showing that paediatric-type stage-adapted B-NHL-derived chemotherapy or anthracycline-based regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-like cycles ± R are very effective in partially resectable disease [6,11,14,17–20,30,31]. Nevertheless, as almost all chemotherapy cycles currently used in paediatric B-NHL still include anthracyclines, alkylating agents and intrathecal-directed therapy, low-intensity chemotherapy for PTFL should ideally be free of the latter compounds, which carry the risk of acute- and long-term toxicity [32–36].

2.1.4. Conclusions

Regardless of the type of therapy, it seems that PTFL does not necessarily require intense multi-drug chemotherapy. Based on the data gained from the EICNHL/i-BFM study on FL, one might infer that in cases of complete resection in carefully defined stage I patients, watchful waiting is justified [14]. If one or two LN, or part of a large node, remain(s), secondary surgery could be attempted. However, it should be emphasized that patients should only be candidates for complete resection, either primary or secondary, if surgery can be performed easily and safely, and most importantly, without any mutilation or risk of long-term morbidity. In all other patients, initial surgery should be restricted to the least invasive procedure to establish the diagnosis, to be then followed by limited chemo- and/or immunotherapy. Given the difficulties in differentiating PTFL from follicular hyperplasia, MZL or LBCL-IRF4, evaluation by specialized hematopathologists is highly recommended before starting any therapy [2,5,11,12,37]. As children with non-resectable PTFL have an excellent outcome with conventional multi-drug chemotherapy, which is, however, associated with acute and long-term toxicity, multinational studies addressing treatment de-escalations have yet to be established. These should consider the current definition of WHO-HAEM5 of PTFL in order to confirm, not only that no chemotherapy is a safe approach in stage I patients with complete resection, but also that low-intensity chemo- ± immunotherapy with anti-CD20 antibody (*i.e.*, anthracycline-free but R-containing B-NHL courses) such as R-cyclophosphamide, vinblastine/vincristine, prednisone (R–CVP), is sufficient for patients with unresectable disease and for patients who do not fulfil the diagnostic criteria of PTFL, such as children with rearrangements involving the *BCL2* or *BCL6* genes [2,5,14,15,31,38–41]. In view of the excellent overall prognosis, local irradiation is not at all indicated in PTFL [2,23,42].

In analogy to PTFL, treatment of LBCL-IRF4 could be resection only in paediatric cases of localised and entirely follicular disease (*i.e.*, tonsils) while others may receive a dose-reduced risk-adapted chemotherapy in prospectively controlled studies [23,29,43].

2.2. Paediatric marginal zone lymphoma

The WHO-HAEM5 subdivides MZL into the following entities: extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), nodal MZL (NMZL), splenic MZL, and primary cutaneous MZL [5]. Importantly, paediatric nodal MZL (PNMZL) is recognized as a distinct entity and discussed separately (Table 2) [5]. PNMZL is a nodal mature BCL and characterised by an interfollicular expansion of clonal marginal B-cells [5]. Since the introduction of PNMZL as a variant of MZL in 2008, the incidence of MZL in children, adolescents and young adults has significantly increased, but overall, still seems to be <2% in childhood NHL [2]. In contrast to EMZL, PNMZL occurs very rarely in patients with pre-existing immunodeficiencies, autoimmune disorders or infections. Data on clinical features, treatment and prognosis of MZL in children and adolescents are limited to small patient series and case reports [23,42,44–61]. As therapy guidelines for childhood MZL have not yet been defined, treatment for both localized and disseminated disease varies considerably [2,42,52,56,59].

2.2.1. Clinical and diagnostic characteristics

Patients with PNMZL typically present with localized (stage I/II) disease, involving LN of the head and neck region [2,23,45,52,56,59]. In contrast, paediatric EMZL is frequently found at sites of mucosa-associated tissues such as salivary glands, the ear-nose-throat area, lungs, digestive tract, and conjunctiva or ocular adnexa [23,46,56,60–62]. Paediatric EMZL has also been reported in the orbit, skin, breast, spleen, kidney, and CNS [23,44,50,51,56,58,63,64]. In order to gain more reliable data in paediatric MZL, the EICNHL and i-BFM Group performed a retrospective multinational study, by which they identified 66 MZL patients [56]. They found that PNMZL displays a male predominance and is often diagnosed in adolescents. Most patients presented without significant symptoms (Karnofsky index of 90–100%) and with normal serum LDH levels. Nevertheless, very rare cases with advanced (stage III/IV) disease were reported, emphasizing the need for complete staging by the IPNHLSS [16,23,42,56].

The site of disease determines the symptoms by which the patients with EMZL present themselves. Most often, local swelling in cases of externally visible tumours or gastric pain in cases involving the stomach are initial symptoms. Several pre-existing conditions have been described in EMZL and might be involved in its pathogenesis. There is an association between EMZL of MALT and autoimmune disorders or immune system dysregulation as a result of a chronic infectious stimulus [46,65–68]. For instance, the incidence of EMZL of salivary glands of patients with Sjögren syndrome is reported to be 40-times higher than in the healthy population [47,59,60,66,69]. Specific infectious triggers are observed in association with MALT lymphoma, like *Helicobacter pylori* in the stomach, *Chlamydia psittaci* in the ocular adnexa, *Campylobacter jejuni* in the small intestine, and *Borrelia burgdorferi* in the skin [46,59,67,68,70–72]. Unlike PTFL, reports of MZL have also been linked with cancer predisposition syndromes [2,52,56,59,60,73,74].

The accurate diagnosis of MZL is challenging. While the histological pattern overlaps with inflammatory conditions and other BCL, especially PTFL, specific immunophenotypic or genetic biomarkers are still missing. Therefore, MZL must be diagnosed by specialized hematopathologists considering the essential and desirable diagnostic criteria of WHO-HAEM5, in close correlation with the clinical information and patient's history (Table 2) [5]. Examinations of BM for cytomorphology and minimal disseminated disease, as well as of the cerebrospinal fluid (CSF) are recommended for at least EMZL, because there are known cases with disseminated disease [52,56,75–80]. Whether analysis of the BM and CSF is needed in PNMZL (as defined by the WHO-HAEM5) is a matter of debate but might be waived [5].

2.2.2. Histopathology and molecular features

At macroscopic appearance, LN of PNMZL present as enlarged and encapsulated nodes without sclerosis or necrosis. The LN architecture is at least partly effaced by an interfollicular proliferation with markedly expanded pale marginal zones and attenuated sinuses. Characteristically, the follicles are often enlarged, with a disrupted CD23-positive follicular dendritic cell meshwork and IgD-positive mantle cells extending into the GC and resembling progressively transformed GCs. The neoplastic cells are polymorphic B-cell infiltrates composed of small-to medium-sized cells with monocytoid features (round nuclei, pale-staining cytoplasm) and centrocyte-like features (irregular nuclei, scant cytoplasm). Sheets of large cells should not be present and would rather favour DLBCL. The infiltrating cells express BCL2 and CD43. BCL6 and CD10 are typically negative. The proliferation rate is low to moderate. Immunophenotyping usually shows surface light chain-restricted $CD19^{+}$, $CD20^{+}$, $CD10^{-}$ B-cells in both PNMZL and atypical marginal zone hyperplasia. Molecular testing for *IG* heavy and light chain-rearrangements are therefore mandatory for the differential diagnosis. The distinction between MZL and PTFL cannot always be accomplished unambiguously. However, clonality assessments contribute to the diagnosis by helping to distinguish benign lesions, such as marginal zone hyperplasia and rare potentially inflammatory lymphoproliferations, from true MZL [22,55,81].

Like in NMZL, trisomy 18 has been found in 21% of PNMZL cases, with 1 case carrying concomitant trisomy 3. Trisomy 13, monosomy 20, and rearrangements of the *IGH* gene with an unknown partner gene have also been detected in single cases [55,81]. PNMZL lacks the t(14;18) (corresponding to *IGH::MALT1*) as well as *BCL10*- or *FOXP1*-involving translocations [5].

2.2.3. Therapy and outcomes

According to the data available, most patients with limited stage PNMZL underwent watchful waiting after complete resection [2,23,52,56,59]. Less than 5% of them relapsed but were cured with second-line therapy. Five-year EFS and OS were 94% ± 6% and 100%, respectively, for the 21 PNMZL patients (17 treated with complete resection only) of the EICNHL/i-BFM study [56]. This indicates that watchful waiting can be followed at least after complete resection. As for PTFL, it should be emphasized that patients should only be candidates for complete resection if it can be performed easily and safely, and without mutilation or risk of long-term morbidity. Primary systemic therapy might be restricted to advanced disease or relapse/progression, which both, in turn, are very rare. If one or two LN, or part of a large node, remain(s), then secondary surgery can be considered, given that complete resection will not cause morbidity in the patient. Anecdotal observations of a few patients suggest that a period of delay before considering systemic therapy might be appropriate for incompletely resected localised PNMZL [52]. Only a few patients with PNMZL have been primarily treated by local irradiation or systemic polychemotherapy; none of them relapsed [2,23].

Heterogeneous treatment approaches and underlying immunodeficiencies in a substantial portion of patients complicate straightforward conclusions from reports on paediatric EMZL. Some patients received stage-adapted polychemotherapy ± R ± radiotherapy (RT), others underwent watchful waiting after complete resection [52,56]. Relapse was reported in 15–35% of patients, but most probably this is rather related to the underlying immunodeficiency than to the therapy chosen [52,56]. Five-year EFS and OS were 64% ± 11% and 97% ± 3%, respectively, for the 44 EMZL patients (9 treated with complete resection only) of the EICNHL/i-BFM study [56]. Altogether, no patients with EMZL died from the lymphoma itself, indicating that for EMZL, limited therapy might be a valuable option for first-line treatment [56]. For completely resected localized disease, watchful waiting could be considered, while R or reduced-intensity chemo- and immunotherapy (*i.e.*, anthracycline-free but R-containing B-NHL courses, R–COP or R–CVP) could provide a good chance for cure not only for patients with limited incompletely resected disease (and no secondary resection possible), but also for advanced disease [38–41]. The approach of antibiotics followed by R for not-completely resected disease could be chosen for typical *Helicobacter pylori*-associated gastric MALT lymphoma [46,52,56]. Nevertheless, due to the lack of reliable data, the use of antibiotics only in cases of proven infection cannot be generally recommended yet but could be tried in addition to chemo- and/or immunotherapy or even carefully up-front.

2.2.4. Conclusions

Paediatric NMZL is predominantly observed in otherwise healthy male adolescents. They usually present with limited disease in the head and neck area and have an extraordinarily good prognosis with local therapy followed by watchful waiting. For EMZL in children

and adolescents, associations with pre-existing conditions are frequently reported. As advanced diseases are also occasionally seen, complete staging is recommended for EMZL. Localized EMZL may undergo watchful waiting after complete resection, while in view of the good overall survival in not-completely resected localized and advanced EMZL, low-intensity chemotherapy ± R could be an option. Conventional chemotherapy ± R may be reserved for relapse/progression, as most paediatric B-NHL protocols still include anthracyclines, alkylating agents and intrathecal-directed therapy [32–36]. In view of the high cure rates, local irradiation is not at all indicated in paediatric MZL [2,23].

2.3. Primary central nervous system lymphoma

Central nervous system involvement by lymphoma is usually a manifestation of systemic disease. Clinicians are familiar with patients presenting with leptomeningeal involvement or epidural spinal cord compression by metastatic lymphoma. Much less often though, young patients will present with lymphoma arising primarily within the CNS, a condition known as primary CNS lymphoma (PCNSL). Given its rarity in paediatric and adolescent patients, we still lack information regarding epidemiology and pathogenesis of this disease, except by the exquisite predisposition among immunocompromised patients, and association with HIV and/or EBV infections [82,83]. In terms of treatment and outcomes, there is some evidence that paediatric PCNSL (pPCNSL) has better long-term outcomes than the adult counterpart, suggesting potentially different disease biologies. However, literature is scarce. It is important to mention that the WHO-HAEM5 has aggregated PCNSL to aggressive B-cell lymphomas arising from the vitreoretinal compartment or from the testes of immunocompetent patients, as a primary large BCL of immune-privileged sites [5].

2.3.1. Clinical and diagnostic characteristics

The clinical manifestations of pPCNSL simulate any other entity characterized by expanding lesions within the CNS, and symptoms are related to its location and size. Given how aggressive PCNSL usually is, patients will report days to few weeks of history at presentation [84]. Symptoms of increased intracranial pressure, palsies, altered mental status, seizures, visual changes, panhypopituitarism have all been reported [85]. Lesions can be single or multiple, with pPCNSL patients usually presenting with tumours localized to frontal and parietal lobes, cerebellum, hypothalamus, and pituitary stalk [85]. Isolated leptomeningeal involvement in pPCNSL also has been reported [84,85].

Initial work-up for staging follows standard procedures [16]. It is suggested to include dedicated neuroimaging (craniospinal MRI or CT with/without contrast), ophthalmologic evaluation, and lumbar puncture, in addition to standard systemic evaluation of disease with contrast-enhanced chest, abdomen, pelvis with/without contrast CT or MRI, and/or whole-body PET-CT/PET-MRI if available, and BM evaluation. Cerebrospinal fluid will show elevation of protein, reactive lymphocytes, but rarely tumour cells. Immunohistochemistry or *IG* gene rearrangements of CSF can detect monoclonal lymphoma cells in lymphoblastic and mature B-cell PCNSL, and elevation of CSF soluble CD27 has been considered a diagnostic marker in adult PCNSL [86,87]. As expected, diagnostics are dependent on tumour location and/or neurosurgery experience, with stereotactic, leptomeningeal, or open biopsy methods available.

2.3.2. Histopathology and molecular features

Adult PCNSL is a B-cell malignancy. In fact, the 2017 WHO classification recognized CNS DLBCL as PCNSL [88]. In a similar way, most paediatric cases are high-grade lymphomas, mainly large BCLs [84,85,88]. However, other histologies have been reported. In a retrospective cohort of 43 pPCNSL cases, 30% were DLBCL, followed by ALCL (21%), LBL (16%), BL (12%), among others (11%) [85]. A larger retrospective cohort of pPCNSL reported by the EICNHL, i-BFM Group and selected North American centres reported 75 pPCNSL cases, also finding most of them to be high-grade BCLs [68%, including DLCBL, BL, B-NHL, not otherwise specified (NOS)] followed by ALCL (23%) [84].

In terms of molecular features, studies evaluating genomic changes in adult PCNSL samples have found abnormalities involving the NF-κB pathway with frequent mutations/deletions involving *MYD88*, *CD79B*, *PRDM1*, *CDKN2A*, and *HLA* cluster [89–91]. Interestingly, a recent study evaluating the whole-genome and transcriptome landscape of adult PCNSL-DLBCL *vs.* systemic DLBCL characterized distinct expression profiles and translocation patterns [92]. Cases of PCNSL-DLBCL were characterized by recurrent alterations in JAK-STAT, NKκB, and B-cell receptor signalling pathways (mutations in *MYD88*, *L265P*, *CD79B*, and *CDKN2A*). Samples from EBV + PCNSL were marked by mutations more restricted to *IG* and *HLA-DRB* loci [92].

Interestingly, a recent study using samples from younger (not immunocompromised) patients (<40 years of age; n = 12) with PCNSL performed next-generation DNA sequencing and genome-wide copy number analysis and compared them with results from samples of PCNSL patients ≥40 years (n = 6) [93]. Two distinct signatures were found named by the authors as "paediatric-type, *MYD88*-wildtype" (n = 8, median age 14 years) and "adult-type, *MYD88*-mutant" (n = 10, 4 of those occurring in young adults). "Paediatric-type, *MYD88*-wildtype" tumours were characterized by alterations involving *GNA13*, *NFKBIE*, *TP53*, *JAK2, CD246* (PD-L1), *EZH2* p.Y646 N, and *GATA2*. Interestingly, survival was significantly better for patients harbouring tumours with "paediatric-type, *MYD88*-wildtype" profiles [93].

2.3.3. Therapy and outcomes

Primary CNS lymphoma is considered an aggressive malignancy with guarded prognosis. Most current 5-year survival for adult PCNSL in the US is about 30% [94]. However, paediatric patients affected by PCNSL seem to have a clearly better outcome than older patients [42,84,95–97]. A cohort gathering 75 pPCNSL cases (all histologies included) to investigate outcomes found a 5-year EFS and OS of 74% ± 5% and 85% ± 4%, respectively [84]. Importantly, there was great variation in treatment approaches across institutions from Europe and North America. Most patients received NHL-subtype-directed chemotherapy (77%), while the remainders received

miscellaneous therapy. The majority of patients received chemotherapy only, while 20% received a combination of chemotherapy and anti-CD20 monoclonal antibody therapy with R (study time span 1991–2019). Radiation therapy (dose range 18–45Gy) was administered in combination with chemotherapy ± R in one third of the cases. Most paediatric regimens included high-dose methotrexate, high-dose cytarabine, anthracyclines, alkylating agents, and tripe intrathecal chemotherapy ± RT. Addition of R did not correlate with improved outcomes in this cohort of patients. Relapse/progression of disease were the most common cause of death [84]. Table 3 summarizes published retrospective cohorts of pPCNSL cases.

3. Mature T-cell and NK-cell neoplasms

3.1. Peripheral T-cell lymphoma, not otherwise specified

ALK-positive ALCL is the most common form of mature T-cell neoplasm in paediatric and adolescent patients. Excluding cutaneous forms of T-cell lymphoma (TCL), other T/NK-cell entities are considered of rare or exceedingly rare occurrence in children. Herein, we will not review hepatosplenic, subcutaneous panniculitis-like, enteropathy-associated or angioimmunoblastic TCL, but only PTCL NOS and ENKL [2,98–100].

The PTCL, NOS incidence in patients <21 years has been reported to be only 0.34 (95% CI 0.27–0.41) cases/million population*year in the US [21], which makes this disease difficult to study in a systematic way in the paediatric setting. Moreover, establishing the diagnosis of PTCL, NOS *per se* is challenging. This is a neoplasm considered by the WHO to be of exclusion, meaning all the other specifically defined mature TCL entities must be excluded first [88]. Importantly, the WHO-HAEM5 separated nodal T-follicular helper (TFH) cell lymphoma and primary nodal EBV + T/NK-cell lymphoma from PTCL, NOS, being the second one being considered a provisional entity [5]. Treatment studies most commonly group patients with PTCL, NOS with others such as ALCL and nodal TFH cell lymphoma. In addition, most of our current knowledge for this disease is derived from adult studies, especially regarding molecular features and best treatment approaches for this orphan population of patients.

3.1.1. Clinical and diagnostic characteristics

Clinically, PTCL, NOS is an aggressive lymphoma that can present with nodal and/or extranodal manifestations [98,99]. Most

Table 3
Overview of selected studies of paediatric primary central nervous system lymphoma.

Reference	N	Age, years; median (range)	Disease subtype	Treatment	Disease status	Outcome
Attarbaschi et al., *2019* [84]	75	12.5 (1.2–18.9)	DLBCL (N = 37), BL (N = 9), MBCL-NOS (N = 5), ALCL (N = 17), PTCL (N = 2), EMZL (N = 1), other (N = 7), Pre-existing conditions (N = 14)[#]	HD-MTX (N = 68), HD-ARAC (N = 55), anthracyclines (N = 59), alkylating agents[a] (N = 64), RT[b] (N = 26); IT (N = 69), R (N = 17) Consolidation with ASCT (N = 3), Allo-SCT (N = 1)	CR1 (N = 53), CR2 (N = 5), CR not yet achieved (N = 5)	5y-EFS 74% ± 5%, 5y-OS 85% ± 4%[@]
O'Suoji et al., *2016* [42]	5	13 (6–16)	DLBCL (N = 2), ALCL (N = 2), other (N = 1). Immunodeficiency (N = 1)	N/A	N/A	100% (median follow-up 2 years, range 1.2–3.0 years)
Thorer et al., *2014* [96]	17	13.3 (1.3–17.9)	MBCL (N = 11), ALCL (N = 5), PTCL (N = 1)	NHL-BFM (N = 11) Chemotherapy + RT for ALCL patients	N/A	3y-OS 63% ± 12% for entire cohort; 3y-OS 92% ± 8% for immunocompetent patients only
Yoon et al., *2012* [97]	6	10.1 (23 months-11.9)	DLBCL (N = 3), BL (N = 2), B-cell lymphoma, undifferentiated (N = 1)	IT (N = 6), CCG-5961/Group C (N = 5), CCG-106B (no HD-MTX) (N = 1)	CR (N = 5)	5y-OS 83.3%
Abla et al., *2011* [95]	29	14 (2–21)	DLBCL (N = 20), ALCL (N = 5), LBL (N = 2), Burkitt-like lymphoma (N = 2). Immunodeficiency (N = 3)	MTX-based (N = 27), non-MTX based (N = 2), chemo-immunotherapy (N = 2), chemotherapy + RT (N = 9), ASCT (N = 2)	ORR 86% CR (69%) PR (17%)	2y-PFS 61% (95%CI, 40–76%); 2y-OS 86% (95% CI, 66%–94%)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; BL, Burkitt lymphoma; MBCL-NOS, mature B-cell lymphoma, not otherwise specified; ALCL, anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma; EMZL, extranodal marginal zone lymphoma; HD-MTX, high-dose methotrexate; HD-ARAC, high-dose cytarabine; RT, radiation therapy; IT, intrathecal; R, rituximab; ASCT, autologous stem cell transplant; Allo-SCT, allogeneic stem cell transplant; CR, complete remission; EFS, event-free survival; OS, overall survival; LBL, lymphoblastic lymphoma; ORR, overall response rate; PR, partial response; PFS, progression-free survival.

[#]Preexisting conditions included immunodeficiency (N = 11), hematologic malignancy (N = 2), and Factor VII deficiency (N = 1).

[#]Preexisiting conditions and number of CNS lesions were associated with inferior outcomes, HD-MTX, HD-ARAC, and alkylating agents were associated with improved outcomes.

[a] Cyclophosphamide was used in 61 patients.

[b] Whole brain radiation therapy at a dose range of 18–45 Gy.

paediatric patients will present with advanced stage disease with BM, liver, spleen, and other extranodal sites (±effusions) involved (Fig. 1) [21,98,99]. Similar to other T-NHL, B-symptoms and haemophagocytic syndrome can be presenting features [88]. Central nervous system involvement is possible and has been reported to occur as pPCNSL, as well [84,96]. Diagnostic work-up and staging procedures follow standard approaches [16].

3.1.2. Histopathology and molecular features

PTCL, NOS histopathology is characterized by heterogeneity with LN architecture being disrupted by an infiltrate (diffuse or paracortical) of variable size lymphoma cells mixed with a polymorphous inflammatory background. However, the diagnosis can only be established by a combination of morphologic and immunophenotypic features that are consistent with mature TCL that does not meet criteria for any other mature TCL [5]. Although the pathophysiology has not been defined, it is postulated that this neoplasm is derived from an activated mature T-cell (likely a $CD4^+$ memory T-cell) [88]. Therefore, its immunophenotype is characterized by an aberrant T-cell phenotype, with variable expression of CD30 [88,98]. In adult PTCL, NOS, two molecular signatures of prognostic significance have been recently described: PTCL-TBX21 and PTCL-GATA3 [101–103]. Patients with PTCL-TBX2 subtype have better outcomes. This tumour is associated with less genomic complexity and higher frequency of alterations of epigenetic modifiers (mostly involved in DNA methylation such as *TET1*, *TET3*, and *DNMT3A*). Contrastingly, the PTCL-GATA3 genotype is linked to guarded prognosis, likely due to greater genomic complexity and alterations involving *TP53*, *PTEN*, *RB1*, *CDKN2A/B*, *STAT3*, *MYC*, *FAT1*, among others [101].

The molecular features driving PTCL, NOS in children and adolescents are less known. Au-Yeung et al. performed mutation analysis (by targeting sequencing approach) in 20 PTCL, NOS samples from patients <18 years [104]. Most cases were marked by at least one variant detected, being *TET2* the most altered gene (30% of the cases), followed by *KMT2C* (25%), *PIK3D* (10%), and *DMNT3A* (10%). *PHIP*, *JAK1*, *JAK3*, and *SET2* were mutated in 1/20 cases, respectively. *TET2* c.86C > G p.Pro29Arg mutation, not previously described

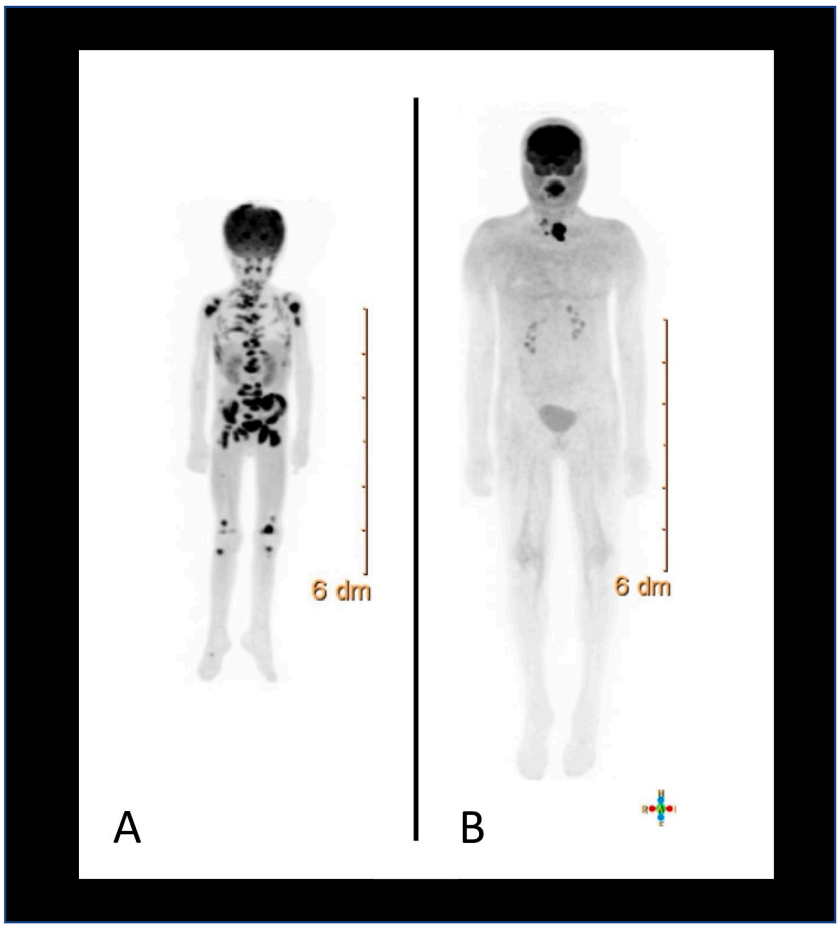

Fig. 1. Paediatric PTCL, NOS usually presents as advanced disease with nodal or extranodal involvement. **Panel A**. Six-year-old male with history of difficulty in walking due to pain. Tissue biopsy revealed PTCL, NOS. Whole-boy PET-CT scan revealed extensive bony involvement of skull, thoracic spine, humeri, rib cage, pelvic bones, greater trochanter, and distal femur. No adenopathy or visceral involvement was noted. **Panel B** Eleven-year-old female with history of difficulty in breathing. Tissue biopsy revealed PTCL, NOS. Whole body PET-CT scan revealed paratracheal nodal involvement. No extranodal areas were involved.

in adult PTCL, NOS was found in 3/6 cases with *TET2* mutations. Interestingly, *TP53* or *RHOA* mutations were not found in any sample. They also detected lower levels of PD1 expression; their data suggest that PTCL, NOS molecular features might vary depending on age of occurrence [104]. A case of PTCL, NOS in a young child with underlying *STAT3* mutated hyperimmunoglobulin E syndrome [105] and one with rhabdoid tumour predisposition syndrome (type III distal 22q11.2 microdeletion including *SMARCB1*) (*personal communication*) have been noted, too.

3.1.3. Therapy and outcomes

Treatment approaches for paediatric patients with PTCL, NOS vary considerably, likely reflecting treating physician experience and lack of literature data. The Children's Oncology Group (COG) Rare and Cutaneous NHL registry reported 9 cases of PTCL, NOS who received 8 therapy approaches [42]. From adult literature, the International T-cell Lymphoma Project demonstrated that the use of anthracycline-containing regimens was not associated with an improved outcome [106]. The German High-Grade NHL Study Group reported improved outcomes for patients treated with an anthracycline-based regimen (CHOP) plus etoposide, comprising patients from 7 different prospective trials [107]. According to the results of their retrospective study ($n = 60$; 5-year EFS: 47% $\pm$ 7%, OS: 56% $\pm$ 7%; $n = 15/60$ with a pre-existing disorder), the EICNHL recommends a block-like ALCL-derived chemotherapy regimen, with an acute lymphoblastic leukaemia-type therapy being the second choice [98,99]. For patients with CD30-positive PTCL, NOS, the addition of anti-CD30 receptor-directed therapy with brentuximab vedotin to chemotherapy has shown to increase overall response rate and survival [108,109]. The role of consolidative stem cell transplantation (SCT) (allogeneic *vs.* autologous) is still debatable but there is evidence that it could improve survival, especially in the advanced setting [110,111]. Several Phase I/II/III studies have been published recently studying new potential drugs to treat adult *de novo*/relapsed PTCL-NOS [112]. A mature (non-anaplastic) T/NK-cell lymphoma-focused clinical trial for children, adolescents, and young adults is currently ongoing (NCT03719105).

3.2. EBV-positive NK/T-cell lymphomas

Under this category of EBV-driven lymphomas we now have two main entities per WHO: (*i*) EBV-positive nodal T/NK-cell lymphoma (not previously included, rather classified as PTCL, NOS), and (*ii*) ENKL (previously ENKL, nasal-type) [5]. The reclassification highlights the fact that EBV-positive T/NK-cell lymphoma has distinct histologic features (resembling more DLBCL) and genetic landscape, with frequent mutations in *TET2*, *PIK3CD*, and *STAT3* [88,113]. Here, we will solely focus on ENKL.

3.2.1. Clinical and diagnostic characteristics

Extranodal NK-cell lymphoma is an aggressive neoplasm of rare occurrence in non-Asian areas/population, except for certain geographic pockets in Central and South America [114]. The disease distribution likely reflects the strong association between EBV infection and ENKL. More often ENKL affects middle-aged people, being very uncommon in children and adolescents [21,112]. The typical clinical presentation is of involvement and destruction of nasopharynx structures and/or other areas of the head or neck. The disease can have nodal involvement, can disseminate to CNS and affect other areas of the body, including BM. Therefore, standard staging methods are to be followed in this condition [16]. Haemophagocytic syndrome is common at presentation of advanced stages/disease recurrence and can be considered as a paraneoplastic manifestation of ENKL [115]. Importantly, EBV-DNA by polymerase chain reaction (PCR) is detected in ENKL patients' serum and is an important marker of disease activity and dissemination [116].

3.2.2. Histopathology and molecular features

A striking feature of ENKL is its histology. The pathology findings give little clue about lymphoma, due to marked tissue necrosis. In fact, the diagnosis can only be established after considering the patient's clinical picture. The tissue destruction is angiocentric, angioinvasive and infiltrated by small, medium-sized or pleomorphic large cells. EBV-encoded small RNA *in situ* hybridization (EBER-ISH) is always positive. The postulated normal cell compartment is a $CD56^{bright}$ activated NK-cell, but rarely a cytotoxic T-cell. Therefore, the immunophenotype will reflect that, with neoplastic cells being surface CD3–, $CD2^{+}$, CD5–, $CD56^{+}$, and cytoplasmic CD3+/–. Less commonly, ENKL cells express a cytotoxic T-cell phenotype being $CD5^{+}$, $CD8^{+}$, and T-cell receptor^{+} [88]. These two cellular origins are indistinguishable by conventional immunohistochemistry of pathology.

The mechanism of EBV lymphomagenesis in ENKL is not completely understood. EBV usually resides in lymphoma cells as an episome. Frequent focal EBV genome deletions and integrated EBV fragments in the host genome in ENKL patients have been demonstrated [117]. Viral integration and expression of latent products, such as LMP-1, promote cell division, migration, and inhibit apoptosis. This process leads to activation of multiple signaling pathways – MAPK/ERK1/2, JAK/STAT, NF-κB, PI3K/Akt – and upregulation of survivin, MYC, soluble IL-2 receptor alpha, and programmed death protein ligand 1 (PD-L1) expression [118].

3.2.3. Therapy and outcomes

ENKL is a cancer model for Multi-Drug Resistance (MDR) studies. The *MDR1* (*ABCB1*) encodes the large and well-known transmembrane protein P-glycoprotein (P-gp). P-glycoprotein expression has been normally found in a variety of human (normal and cancer) cell membranes, functioning as a drug-transport efflux pump. Expression of P-gp has been linked to intrinsic or acquired resistance to drugs such as anthracyclines, vinca alkaloids, or epipodophyllotoxins in hematological malignancies, such as ENKL [119]. Therefore, commonly used lymphoma treatment regimens such as CHOP or CHOP-like cycles do not produce satisfactory results.

Radiation has been the mainstay of limited stage ENKL, but currently chemoradiotherapies including platinum are recommended [120–122]. The use of therapeutic agents that are not affected by the P-gp mechanism, such as L-Asparaginase, has impacted positively

the outcome of those patients. L-Asparaginase-based regimes such as modified SMILE, DDGP, P-GEMOX, or Aspa/Met/Dex should be considered as up-front therapy for ENKL patients, especially in advanced settings [112].

Overexpression of PD-L1 offers another therapeutic approach for those patients. PD1 immune checkpoint blockade with pembrolizumab or nivolumab has been used in relapsed/refractory (r/r) ENKL [123,124]. Tian et al. recently published a retrospective cohort of 26 cases of r/r ENKL treated with PD1 blockade alone (sintilimab or camrelizumab) or in combination with chemotherapy. They obtained disease control in 73.1%, with an objective response rate of 50%. The 1-year PFS and OS were 23.1% and 54%, respectively, with low rates of grade 1 or 2 immune-related adverse events. Persistence of EBV PCR load after PD1-blockade was associated with poor outcomes [125]. Like in PTCL, NOS, the role of (allogeneic) SCT as consolidative therapy is still in debate but likely beneficial to patients with advanced stage disease [111]. In the paediatric setting, there is no prospective data on ENKL treatment, so enrollment in clinical trials designed to this group of patients is highly encouraged (NCT03719105).

4. Summary

In this review, we discussed a variety of clinically and pathologically distinct NHL entities that are of rare/very rare occurrence in paediatric/adolescent patients. Of note, the B-cell NHL subtypes tend to have a favorable outcome with minimum or no therapy, in contrast with the T/NK-cell variants that overall respond poorly to treatment, translating to reduced OS rates. The reasons for the discrepancies in disease behavior and response to therapy remain largely unknown. The most obvious explanation would be the rarity of those diseases that make them difficult to study separately from other lymphomas such as ALK-positive ALCL. For having orphan diseases, patients with rare forms of NHL end up receiving therapies that do not apply for their disease simply because of the lack of clear, systematic (biology or therapy) data. Recognizing that rare NHL in children and adolescents are distinct diseases will help us to develop protocol therapies that are applicable to them. Thus, developing and enrolling patients in clinic trials specifically designed for those patients will likely promote improvements in outcomes, especially for patients with rare forms of T/NK-cell lymphoma.

4.1. Practice points

- PTFL is a distinct WHO B-cell neoplasm characterized by nodal involvement, indolent clinical course, lack of *BCL2-, BCL6-* or *C-MYC* rearrangements, and overall excellent prognosis with limited treatment. It should be differentiated from LBCL-IRF4, which is also a distinct WHO entity with a good prognosis.
- MZL in children and adolescents can have distinct presentations as nodal (paediatric nodal MZL) or extranodal disease (extranodal MZL). Both entities have excellent outcomes with limited treatment.
- Unlike adult PCNSL, paediatric PCNSL can present with different histologies other than DLBCL and responds rather well to histologic NHL subtype-directed polychemotherapy. In addition, paediatric PCNSL outcome seems to be better than in adults, suggesting distinct disease biologies (*i.e.,* "adult-type, *MYD88*-mutant" *vs.* "paediatric-type, *MYD88*-wildtype").
- Paediatric PTCL, NOS is an aggressive T-cell neoplasm of guarded outcome. The molecular features driving this disease are unknown, and there is no defined standard therapy in the paediatric setting.
- Extranodal NK-cell lymphoma is an EBV-associated lymphoid malignancy characterized by P-glycoprotein overexpression, and PD-L1 upregulation. The use of L-Asparaginase-based regimens has improved the ENKL outcomes, but no defined standard therapy has been established for paediatric patients.

4.2. Research agenda

Improving knowledge in clinical, biological and treatment aspects of rare forms of paediatric NHL.

- Systematic acquisition of clinical data to understand disease behaviour in children and adolescent with rare forms of NHL.
- Development of multi-institutional tissue banks for use in research directed for better understanding of histology, immunophenotype, and genome of rare paediatric NHLs.
- Focus on national and international collaboration to implement clinical trials designed for young patients with rare subtypes of NHL.

Authorship contributions

ACX, RS and AA wrote the paper. All authors provided substantial contributions to this review, drafted and critically revised the manuscript, and approved the final version for publication.

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