# Non Hodgkin Lymphoma Among Children: Pathological Aspects and Diagnostic Challenges

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Sabrine Derqaoui[1,2], Ismail Boujida[1,2], Oussama Marbouh[2,4], Lamiaa Rouas[1,2], Laila Hessissen[2,3] and Najat Lamalmi[1,2]

[1]Department of Pathology, Children's Hospital Ibn Sina University Hospital, Rabat, Morocco. [2]Faculty of Medicine and Pharmacy of Rabat, Mohamed V University, Rabat, Morocco. [3]Center of Pediatric Hematology and Oncology, Children's Hospital Ibn Sina University Hospital, Rabat, Morocco. [4]Department of Pediatric Surgery A, Children's Hospital Ibn Sina University Hospital, Rabat, Morocco.

**ABSTRACT:** Non-Hodgkin lymphoma (NHL) are common malignancies in children. Available data on clinico-pathological aspects of pediatric NHL in developping countries are limited and diagnostic approach appears more delicate with absence of molecular studies. The objectives of our study are: analyzing the pathological spectrum of NHL among children and highlighting challenges in the diagnosis including: limited biopsic material; unusual subtyptes, age group, or localization. We retrospectively analyzed clinico pathological characteristics of 101 NHL's cases among children diagnosed in the Pediatric's pathology unit over a period of 4 years There were 78 (77.2%) male and 23 (22.8%) female. The median age was 7.2 years. The most common histologic subtypes of NHL were Burkitt lymphoma in 65 patients (64.4% ); followed by lymphoblastic lymphoma in 22 patients, large B-cell lymphoma in 9 patients ( 8.9%); anaplastic T cell lymphoma in 3 patients; NOS mature T cell lymphoma and pediatric type follicular lympoma in 1 patient each. In conclusion, this study Morocco illustrates the pattern of distribution of NHL and emphasizes challenges in the diagnosis of these neoplasms.

**KEYWORDS:** Non hodgkin lymphoma, histopathology, pediatrics

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**CORRESPONDING AUTHOR:** Sabrine Derqaoui, Department of Pathology, Children's Hospital Ibn Sina Teaching Hospital, Abderrahim Bouabid Avenue, Rabat, 12000, Morocco. Email: s.derqaoui@gmail.com

## Introduction

Non-Hodgkin lymphoma (NHL) are lymphoproliferative disorders accounting for the fourth most common malignancy in children.[1] Most of NHL among pediatric population, in contrast with their adult counterpart, are high grade with frequent extranodal localizations. The current WHO classification recognizes different subtypes with distinct morphologic, immunophenotypic, and genetic features.[1,2] Thus, an accurate diagnosis is based on integrating all these informations. The main NHL pathologic subtypes in children include: Burkitt's lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), T or B lymphoblastic lymphoma and anaplastic large-cell lymphoma.[1,3] In the current literature, available data on clinico-pathological aspects of NHL among children in developing countries are limited.[3] Furthermore, diagnostic approach appears more delicate because of the absence of molecular studies in these regions (including morocco). We retrospectively studied the clinical and pathological characteristics of pediatric patients with NHL diagnosed in the department of Pediatric's pathology unit over a period of 4 years (between 2017 and 2020) to enable our results with comparison with worldwide data.

**The objectives of the present study are** analyzing the spectrum of NHL among children over a period of 4 years and highlighting challenges in the diagnosis of these tumors

## Material and Methods

Our study is a descriptive retrospective study of clinico pathological features of NHL among pediatric population diagnosed on biopsies and cytology specimen in the Department of Pediatric's Pathology of Ibn Sina hospital university center, over a 4-year period (from January 2017 to December 2020). We have included in the study non Hodgkin lymphoma, of all anatomical sites, in patients aged under 16 years old. We have analyzed epidemiologic characteristics including: (1) age, (2) gender, (3) site of location (4) staging (according to the Ann Arbor staging system) and pathological features including: morphology and immunophenotype. For biopsies, formalin—fixed, paraffin-embedded and Hematoxylin and eosin stained sections were analyzed. Lymphoma's subtyping was performed by using a panel of monoclonal antibodies on IHC CD2 (clone AB75), CD3 (polyclonal), CD4 (clone 4B12), CD5 'clone 4C7),CD7 (clone CBC.37), CD8 (clone C8/144B) CD10 (56C6), CD79a (clone JCB117 ), CD20 (clone L26), CD10 (clone 56C6) CD23 (DAK-CD23), CD30 (clone Ber –H2),CD45(clone 2B11 +PD7/26), CD1A (010), CD138 (MI15) BCL-2 (clone 124), BCL-6 (clone PG-B6p), Cyclin D1 (clone EP12), Ki-67 (clone MIB-1), MUM1( MUM1p), ALK-1(clone ALK1)), and Tdt (clone EP266). For fine needle aspiration, and effusion samples; May grunwald giemsa stained slides were analyzed. Immunocytochemistry was performed

**Table 1.** clinicopathological characteristics of patients.

| CHARACTERISTICS | PATIENTS: NUMBER (N = 101) | PERCENTAGE (%) |
|---|---|---|
| Age: <2 year | 13 | 13.1 |
| [2-10 year] | 66 | 66.7 |
| [10-15 year] | 22 | 22.2 |
| Gender: Male | 78 | 77.2 |
| Female | 23 | 22.8 |
| Primary site: Abdomen | 50 | 49.5 |
| Pleura and mediastinum | 19 | 18.7 |
| Head and neck | 15 | 14.8 |
| Peripheral lymph nodes | 13 | 3 |
| Bone | 3 | 3 |
| Subcutis | 1 | 1 |
| Histological subtype: | | |
| Burkitt lympoma | 65 | 64.4 |
| Lymphoblastic lymphoma | 22 | 21.7 |
| Large B cell lymphoma | 9 | 8.9 |
| Anaplastic T cell lymphoma | **3** | 3 |
| NOS mature T cell lymphoma | 1 | 1 |
| Pediatric type follicular lymphoma | 1 | *1* |
| Diagnostic tool: Histology | 61 | 60 |
| Cytology | 40 | 40 |

using the same antibodieson cytospins. Histologic classification was based on the WHO 2016 classification of tumors of hematopoietic and lymphoid tissues. The data were analyzed using a Microsoft® Excel spreadsheet.

## Results

A total of 101 patients were included in this study. Patients characteristics are shown in Table 1. At the time of diagnosis, the median age was 7.2 years, ranging from 10 months to 15 years. The most represented age range was 2 to 10 years (66.7%) while only 13.1% of patients were under 2 years. There were 78 (77.2%) male and 23 (22.8%) female. For disease localization, abdominal involvement was the most common, affecting 50 ( 49.5%) of our patients, followed by mediastinum and pleura in 19 (18.7 %) cases, head and neck in 15 ( 14.8%) cases; peripheral lymph nodes in 13 (13%) cases; bone in 3 (3%) cases and subcutis in 1 (1%) patient. The majority had a stage III (70%); followed by stage IV in 18%. The diagnosis was made in 60% of the cases by histological analysis of fine needle biopsies or mass/lymph node resection; and in 40% of the cases on the cytological examination of abdominal and pleural effusion cytology. The most common histologic subtypes of NHL were BL which affected 65 patients (64.4%); while lymphoblastic lymphoma was documented in 22 patients (20 were of T phenotype, and 2 were of B phenotype). Large B-cell lymphoma was diagnosed in 9 patients (8.9%); anaplastic T cell lymphoma in 3 patients; NOS mature T cell lymphoma in 1 patient and pediatric type follicular lymphoma in 1 patient.

## Clinico-Pathological Features According to Histological Subtype

### *Burkitt lymphoma*

The 65 cases included 54 (83.1%) male and 11 female (16.9%), the median age was 7.6 years, it ranged from 10 months to 15 years. The most common locations were abdominal in 50 (76.9%) patients. On histology, it was a diffuse pattern proliferation with a starry sky appearance and tangible body macrophages. Neoplastic cells were intermediate-to-large lymphoid cells with irregular nuclei, small centrally located nucleoli and a basophilic cytoplasm (Figure 1). Immunophenotype was classic in all patients: CD20 +, CD10+, BCL6+, BCL2-, CD3- ki67 proliferation index was approximating 100% in all cases.

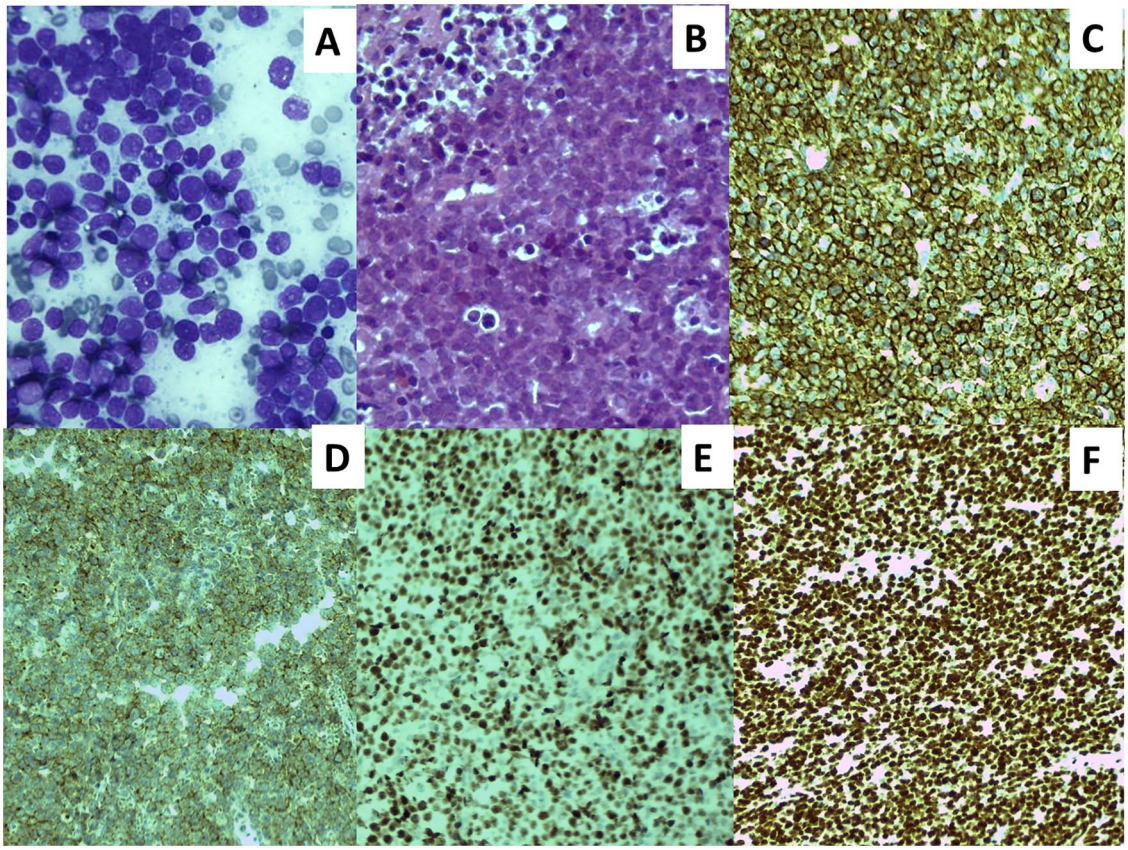


**Figure 1.** Burkitt's lymphoma histology: starry sky pattern, monomorphic lymphoid cells; vesicular chromatin, scant cytoplasm; cytology (A) HEx400 (B). Immunohistochemistry: The lymphoma cells diffusely express CD20 (C), CD10 (D) Bcl6 (E), Ki-67 (F) demonstrate a high (~95%) proliferation rate.

*T Lymphoblastic lymphoma*

The 22 cases included 13 (50.1%) male and 9 female (40.9%), the median age was 8.4 years, it age ranged from 5 months to 14 years. The most common locations were pleura and medisatinum in 19 (86.3%) patients, eyelid, bone and subcutis in 1 patient (4.5% ) for each, respectively. Histology, showed sheets of medium to large blastic cells with finely clumped nuclear chromatin, small or absent nucleoli and scanty cytoplasm with multiple mitotic figures. There was no evidence of maturation. Immunohistochemistry staining showed positivity for: CD3 +(All cases), TDT+(all cases), CD10+ (10 patients), ki67 proliferation index ranged from 80% to 100% in all T LBL cases (Figure 2). And for both cases of B-LBL, CD20 was focally positive, CD45, CD79a and Pax5 were diffusely positive; 15% to 20% of cells expressed TdT and CD10. Proliferation's index with Ki 67 was approximately 80% (Figure 3).

*DLBL*

The median age of 8 patients with DLBL was 6.4 years with age range between 2 and 13 years. 7 (87.5%) cases were male and 1 (12.5%) case was female. 06 cases were located in lymphe nodes and 2 cases in bone. Histology revealed a diffuse pattern proliferation of a centroblast-like cells, with prominant nucleoli, dense chromatine, and multiple mitotic figures. Immunostaining showed positivity for pan B cell markers in all patients, germinal center markers in 5 cases, BCL2 and MYC overexpression in one case. Ki- 67 proliferation index ranged from 40% to 80%.

*Anaplastic large T cell lymphoma*

The 3 patients ages were 8, 12, and 14 years. There were 1 male and 2 females. All the cases had tumors located in lymph nodes. On histology, tumor consists of sheets of medium to large cells with abundant cytoplasm, voluminous nuclei, open chromatin, prominent, and/or multiple nucleoli. Hallmark cells (showing horseshoe/kidney shaped nuclei) were sparse. Mitotic figures and apoptotic bodies were numerous. Neoplastic cells stained positive with CD30, ALK, CD3, and CD5. Pan B markers as well as CD15 and AE1/AE3 were negative (Figure 4).

*Pediatric type follicular lymphoma FL*

The single case of FL occurred in a 10 years-old male. The tumor was located in the eyelid. Histology revealed a follicular pattern proliferation with expansile irregular follicles. Germinal centers contained monotonous medium to large blastoid cells, expressing CD20, CD10, and BCL6. BCL2 was negative.

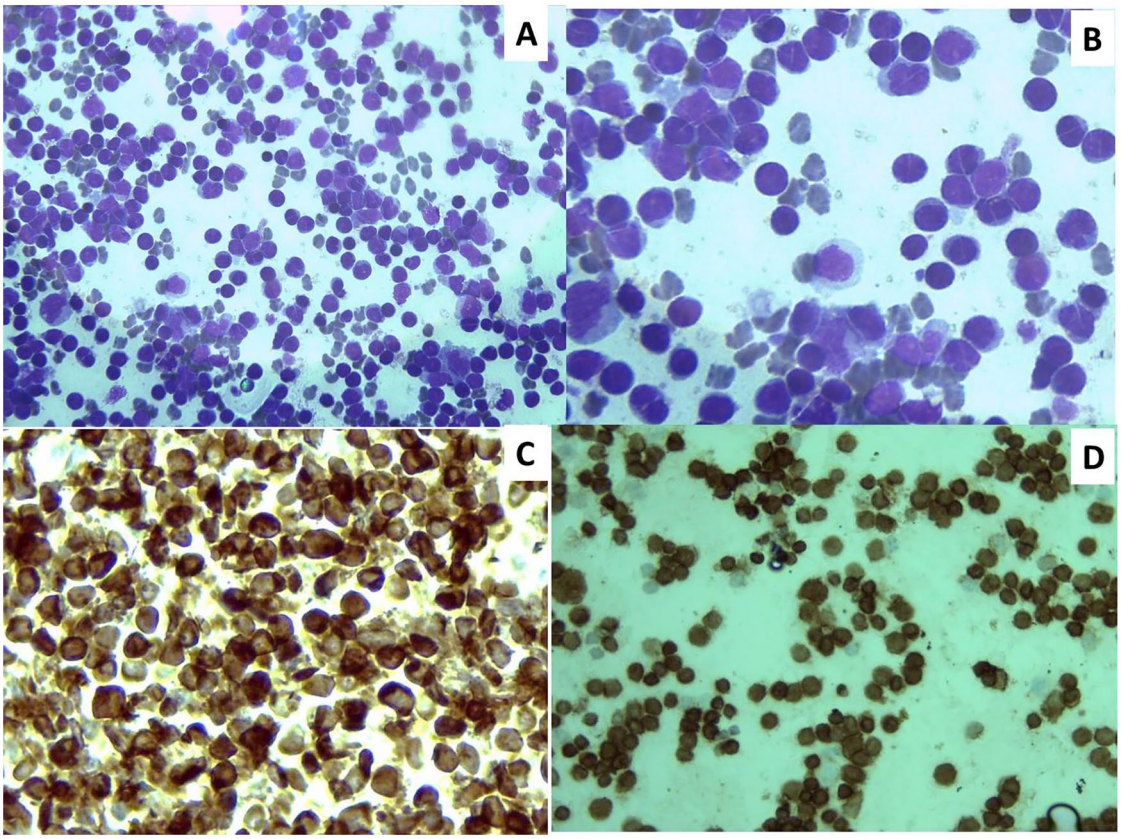


**Figure 2.** Precursor T-lymphoblastic lymphoma cytology: blastic cells with scant cytoplasm, hand mirror appearance, inconspicuous nucleoli, and fine nuclear chromatin. (A) MGG stain × 200; (B) MGG stain ×400. Immunocytochemistry shows positivity for CD3+ (C) TdT+ (D) (×1000, H&E).

*NOS mature peripheral T cell lymphoma*

The single case of NOS mature peripheral T cell lymphoma occurred in a 15-year-old male; in the ileo ceacal lymph nodes. On histology, it was a diffuse proliferation consisting of medium to large sized cells showing moderately propleomorphic nuclei, vesicular chromatin, prominent nucleoli and frequent mitoses. Immunohistochemistry revealed positivity of CD3 CD5 CD2, loss of CD7 expression. CD30, CD15, CD20, PAX5, and ALK. Ki67 proliferation index was estimated at 50%.

## Discussion

*Epidemiology*

NHLs are a heterogeneous group of lymphoproliferations, representing approximately 8% to 10% of all childhood cancers.[3] In contrast to NHL in adults, pediatric NHL are intermediate to high grade neoplasms with frequent extranodal involvment and a clinically aggressive behavior.[1,3] The incidence of histologic NHL's subtypes varies according to age (1) and its frequency has been variably reported worldwide.[4] Our study describes the epidemiological clinical and pathological features of 101 moroccan pediatric NHL. The median age at diagnosis in our study was 7.4 years (ranging from 5 months to 15 years). Our findings are older to the previously reported age in the literature[4-7] which ranges from (6.1 to 6.4 years). NHL in our study affected (64.3%) boys and (35.7%) girls with male to female ratio of 1.8; 1.these results are consistent with previously reported male predominance of childhood lymphoma in different series of the literature.[4]

Pediatric NHL might derive from mature or immature (blastic) cells and might have B or T phenotype.[3] The main pathologic subtypes, in decreasing order of frequency, include: Burkitt lymphomas (BL), lymphoblastic lymphomas (LBL) diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL); while other mature B or T NHL represent rare entities.[1,3] Similar to different series of the literature, BL was the most common subtype in our patients, followed by LBL, DLBL and ALBL.[4-7] Multiple studies are required for the diagnosis of pediatric NHL and for determining prognostic factors; including: morphologic findings (cytology and histology); immunophenotyping (flow cytometry or immunohistochemistry) and genetics.[3]

*Diagnostic tools*

Cytology analysis is a simple diagnostic tool to assess lymphadenopathy; mass lesions or effusions. It is the first line investigation in patients in need of rapid diagnosis and/or presenting with respiratory distress. It is also indicated when

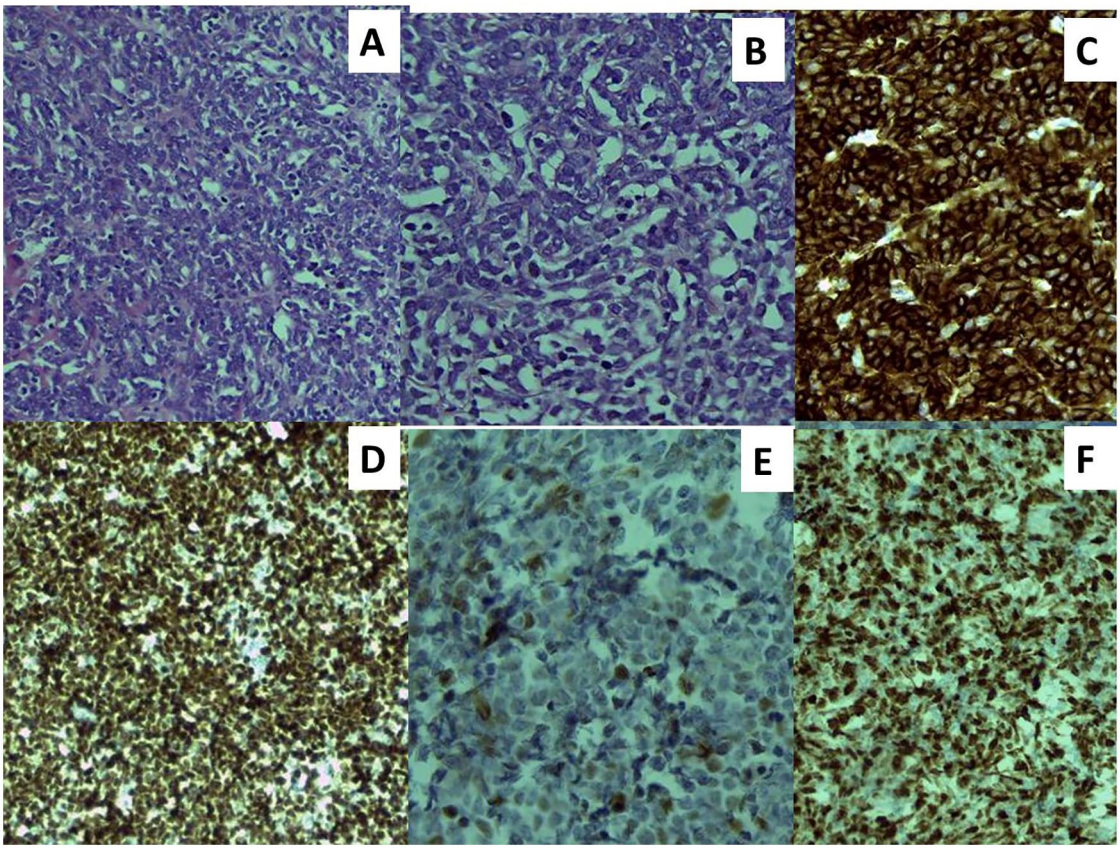


**Figure 3.** B lympoblastic lymphoma histology: diffuse sheets of medium to large blastic cells with granular chromatin, small or absent nucleoli and scanty cytoplasm with multiple mitotic: HEx200 (A), HEx400 (B) immunohistochemistry: LCA+ (C), Pax5+ (D); TDT + in 15% of cells (E); Ki 67: 80% of the cells (F).

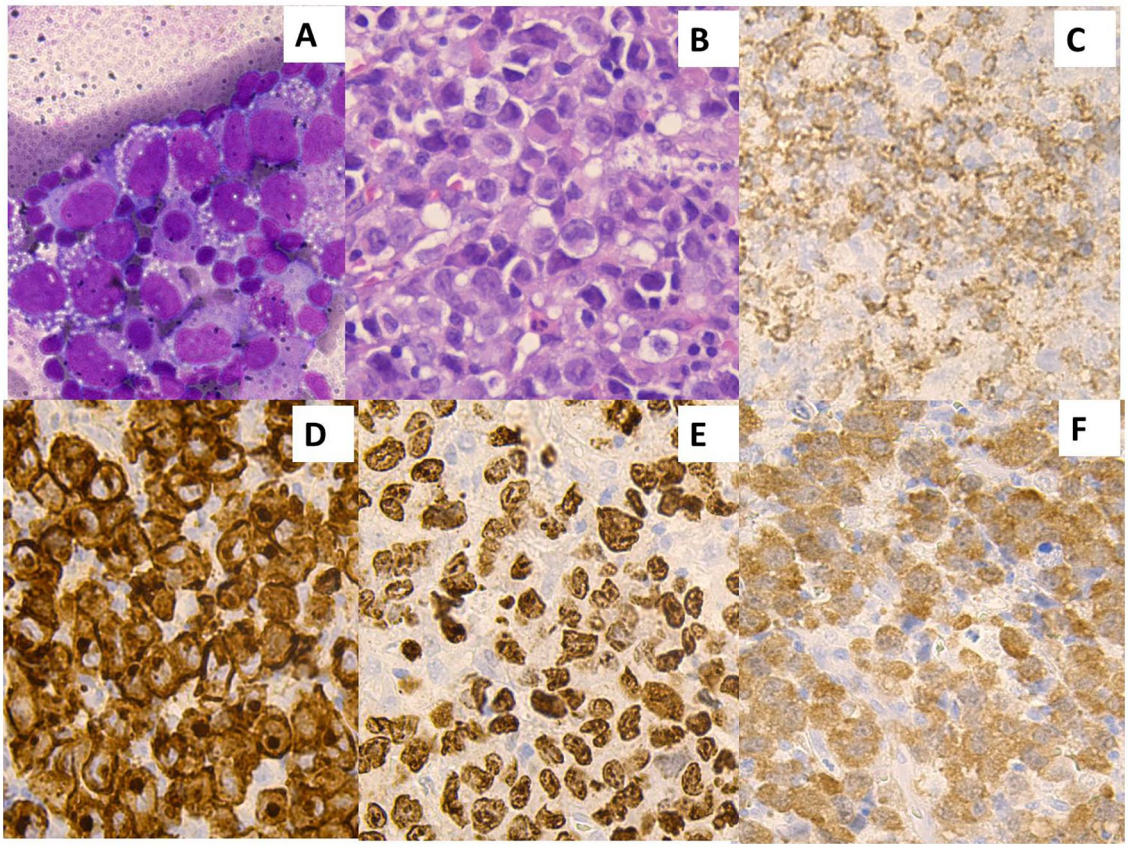


**Figure 4.** Anaplastic large-cell lymphoma histology numerous large tumor pleomorphic cells including REED sternberg cells and wreath-like forms: cytology (A), histology HEx400 (B). Immunohistochemistry staining: CD3+ (C), CD30+ (D), ALK+ (E). and ki67 (F).

biopsy is extremely difficult (eg, mediastinal, retroperitoneal mass).[8] However, morphological analysis is only suggestive of lymphoma, an accurate diagnosis is based on immunophenotyping by either immunocytochemistry or flow cytometry.[9,10] In the present study, cytomorphology complemented by immunocytochemistry provided the diagnosis in 35% of the cases (61% were BL, and 39% were lymphoblastic lymphoma); and adequate therapy has been initiated.

*Dignostic difficulties*

The diagnosis of NHL might be challenging; especially when presenting in unusual localization, age group, or histological subtype.

Fine needle biopsy is a simple, safe and reliable technique without contraindications, in the diagnosis of non-Hodgkin lymphoma. It has been demonstrated that the diagnostic accuracy of this procedure was 91.4% in the study of Asim et al.[11] It provides material for morphologic analysis and other ancillary studies (immunohistochemistry, genetic analysis).[11] However, when the material is limited, the accurate diagnosis becomes difficult, as it needs exhaustive IHC panel to rule out differential diagnosis. Thus, pathological material with optimal quantity and quality is mandatory to allow performing all the required tests for the diagnosis.[13] In our study, the biopsic material was limited in profound localization, thus we had to make limited IHC panel which makes the diagnosis challenging. For abdominal lymphadenopaties; surgical biopsy has been considered as the gold standard procedure, however increased complications, costs and delay in the diagnosis have been reported. Therefore, fine needle biopsy is the recommended technique. Kerviler et al. proposed performing 5 biopsies: 3 formalin fixed fragments and 2 frozen ones for molecular studies.[12]

Unusual histological subtypes are also a diagnostic challenge for pathologists, our series encountered 1 case of NOS T cell lymphoma presenting as multiple ileocecal lymphadenopathies in a 15 years old male. In fact, peripheral mature T cell lymphoma PTCL are a heterogeneous and extremely rare lymphoid neoplasms; making their correct diagnosis in children challenging.[13] In our case, the FNB provided limited material, and the diagnosis of T lymphoid neoplasm was made, without subclassifying it. The second biopsy was made by laparotomy, a large immunohistochemical panel was made; allowing an accurate diagnosis; as the quantity of pathological material was optimal.

Primary non-Hodgkin's lymphoma of bone in children represents a rare condition, accounting for only 2% to 9% of cases among NHL. Femur and pelvic bones represent the most common involved sites, and DLBL the most common histological subtype.[14] We have reported in the current study, 3 cases (2 DLBL and 1 T-LBL) presenting as multiple lytic lesions involving iliac bone in a 3; 4 and 6 years old boys. The diagnosis was challenging because of this unusual presentation, a large immunohistochemical panel was made to rule out the other differential diagnosis, including the other round cell pediatric's tumors.

*Pathology and differential diagnosis*

For pathological analysis, optimal fixation, and adequate processing are essential for providing good histologic sections (ranging from 4 to 6 microns thick). When very limited material is available, conservation of the tissue is recommended, by cutting sections for HE and additional studies (immunohistochemistry etc.) at the same time.[3] After including clinical features, morphological analysis allows the pathologist suggesting a diagnosis of NHL based on specific morphologic features. However, additional studies are required for most pediatric NHLs and to rule out differential diagnosis.[3]

As previously reported, BL was the most common subtype in our series. It accounts for approximately 80% of childhood B-NHL. BL generally presents as an advanced-stage disease, involving commonly the abdomen.[1] Morphologically, BL presents as a diffuse proliferation with a starry-sky pattern (reactive tangible body macrophages); characterized by monomorphic medium-sized neoplastic cells with vacuolated basophilic cytoplasm; showing numerous mitotic figures and apoptotic bodies.[15] Two morphologic variants have been described; including: (1) BL with plasmacytoid differentiation and (2) atypical Burkitt/Burkitt-like lymphoma (aBL/BLL) which exhibits greater nuclear pleomorphism.[15] It is important to know, that the "starry sky" pattern lacks specificity, and is seen in other NHL with high proliferating rate.[3] The typical immunophenotype of BL is CD20+/IgM+/CD10+/bcl-2–/bcl-6+ with the Ki-67 proliferation index (PI) nearly at 100%.[15] MYC translocation represent the hallmark cytogenetic alteration of BL.[3] The 2016 WHO classification of lymphoid neoplasms recognizes a new category: Burkitt-like Lymphoma With 11q Aberration, the latter shares the same morphologic and typical immunophenotypic features with BL, but lacks MYC translocation.[16] In the study of Horn et al[17] analysis of 11q is recommended in MYC-negative high-grade lymphomas with BL features, especially when BCL2 is negative and a conspicuous coarse apoptotic bodies are present within macrophages.[17] DLBL represents the main differential diagnosis, especially when exhibiting a very high PI and starry-sky growth pattern or have medium-sized tumor cells showing slight nuclear pleomorphism mimicking those of classical BL.[15]

Lymphoblastic lymphomas are immature lymphoid malignancies accounting for approximately 30% of non Hodgkin lymphoma in children. Most of these neoplasms originate from T cell precursors while less than 25% of them originate from B lymphoblasts.[18] T LBL involves commonly mediastinum, while B-LBL involves to present skin and soft tissue.[3] Our series encountered 20 cases of T LBL and 2 cases of B LBL, the latters present as subcutaneous mass masses The diagnosis

requires identifying blasts; in bone marrow or tissue biopsy.[19] It combines (i) characteristic morphology, (ii) precursor cells positive markers, (iii) with lineage definition, and (vi) subtyping by additional stainings and/or genetic analysis.[19,20] On cytology, lymphoblasts vary from small cells with (1) scant gray-blue cytoplasm, (2) round or convoluted nuclei, (3) with condensed nuclear chromatin without nucleoli; to large cells with a prominent nucleoli, a moderate and occasionally vacuolated cytoplasm.[19,21] Uncommon features include: coarse myeloblasts-like and hand mirror appearance.[21] On immunohistochemistry, T lineage blasts express CD1a, TdT (extremely helpful marker) CD2, CD5, CD7, cytoplasmic CD3 with coexpression of CD4 and/or CD8; CD10 (in 15%-40%). B lymphoblasts are positif for CD19, CD79a CD22, PAX5, TdT, and CD10.[7] Variable expression for CD 34, myeloperoxidase and CD20 has been reported.[3]

Diffuse large B cell lymphoma (DLBCL) is a mature B-cell neoplasm, accounting for 10% to 20% of pediatric NHL.[1] Its biological behavior is less aggressive than its adult counterpart, with a better prognosis.[4] Clinically, DLBL presents more often as a localized disease involving the abdomen, similarly to BL; while CNS or bone marrow involvment are less frequent.[1] On histology; DLBL consists of sheets of large lymphoid cells, morphologically variable, including: centroblastic, immunoblastic, and anaplastic variants.[22] They show positivity for pan B cell markers( CD19, CD20, CD79a, and PAX-5) Ki 67 proliferation index is usually higher 40% to 50% . MYC and BCL2 expression (double expressor DLBL) represents an adverse prognostic factor. It is recommended to asses CD5 expression by imunohistochemistry, as it is associated to a poorer outcome. The most common subtyping system is based on the cell of origin by genetic profiling. It recognizes: germinal-center DLBL type (DLBCL-GC), activated/post germinal center B-cell type (DLBCL-ABC), and unclassified type. Hans algorithm allows by immunohistochemistry the COO's.[23,24] BL represents the main differential diagnosis. Other diagnosis which must be ruled out are, lymphoblastic lymphoma and (who)

Anaplastic large cell lymphoma is a mature T-cell lymphomas accounting for approximately 10% of childhood NHL and for the most common subtype of T-cell lymphoma,[2,25] it represented the fourth most common lymphoma in our series. The frequently involved sites include lymph node, skin and bone, while extension to CNS and bone marrow is uncommon. Most of pediatric ALCL harbor rearrangement of ALK gene.[2] On histology, ALCL exhibits a wide morphological spectrum including: (1) common pattern, (2) small cell variant, (3) Hodgkin-like variant (4) lymhohistiocytic variant and (5) sarcomatoid variant. The common pattern consists of cohesive sheets of hallmark cells; in different proportions, which are defined as large cells with abundant cytoplasm, pleomorphic features, and a horseshoe- or kidney-shaped nuclei. The background and neoplastic cells differ among histological variants all of which show hallmark cells in different proportions.[25,26] The current WHO classification of hematopoietic disorders recognizes ALK-positive (ALK+) and ALK-negative (ALK-) ALCL.[26] thus, On immunohistochemistry, CD30 and ALK's expression represent the diagnostic clue. Pan B cell markers are negative. The differential diagnosis is broad including: ALK positive diffuse large B cell lymphoma with immunoblastic/plasmablastic features, Hodgkin lymphoma, Lymphomatoid granulomatosis, Pleomorphic carcinoma, and reactive non neoplastic lesions.[25]

Our series encountered one case of pediatric type follicular lymphoma (PTFL) which is a distinct clinicopathologic entity recognized in the 2016 WHO classification of tumors of hematopoietic and lymphoid tissues.[26] PTFL accounts for 1% to 2% of pediatric NHL, presenting as a nodal disease commonly in the head and neck region, whereas conjunctival PTFL ( as in our series) is extremely rare. In fact; only 5 cases of conjunctival PTFL have been reported to date, in the English literature.[27]

Histology shows a follicular pattern with expansive irregular borders and attenuated mantle zones and lack of polarization of germinal centers. Back to back arrangement and a « node in node « appearance are common findings. The follicules show a starry sky pattern; consisting of monotonous, medium to large sized blastoid cells with round nuclei, clumped chromatin and small nucleoli.[13]

Immunophenotype of neoplastic cells is: B cell markers +, CD10 +, BCL6+, BCL2-, and IRF4-. Differential diagnosis is broad and challenging, it includes reactive follicular hyperplasia, nodal marginal lymphoma in children, large B-cell lymphoma with IRF4 rearrangement and usual follicular lymphoma. Thus, clonality analysis remains mandatory for the diagnosis of PTFL; however, we lack molecular testings in our instituation.[26]

The last **histological** subtype encountered in our series was NOS T cell lymphoma in a 15 years boy, presenting as multiple ileocecal lymph nodes. The diagnosis was challenging as this entity is exceedingly rare among pediatric population.[13] The largest series in the literature reporting non anaplastic peripheral T cell lymphoma in children and adolescents, NOS T cell lymphoma was the main histological subtype, involving mediastinum and cervical lymph nodes.[28] It is a heterogeneous category considered as a diagnosis of exclusion, being defined as a group of nodal T cell lymphomas that do not meet the diagnostic criteria of one of the other WHO-defined T-cell lymphoma categorie.[23] On morphology, neoplastic cells vary from medium to large atypical cells. The background is polymorphous. Immunophenotypically, most cases most cases show loss of one of the pan T cell markers, have a mature T-cell phenotype, and express one of the major subset antigens: CD4 > CD8. CD30 is often positive. The differential diagnosis is broad, including other peripheral T cell lymphoma (anaplastic large cell lymphoma, extranodal NK/T cell lymphoma etc); Hodgkin lymphoma and non-neoplastic lymphadenopathies such as: paracortical lymphoid hyperplasia.[24]

**In conclusion**, this retrospective study of NHL among children from Morocco illustrates the pattern of distribution of various common and rare histological subtypes; and emphasizes challenges in the diagnosis of these neoplasms.

## Authors' Contributions

All authors read and approved the final manuscript.

## Ethical Statement

This study was an observational study and there was no cost or intervention for the patients, and the data was collected from medical records. Patients information remained confidential.

## ORCID iD

Sabrine Derqaoui https://orcid.org/0000-0002-8935-1346

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