**Prognostic Impact of pathological subtypes in children with Classic Hodgkin Lymphoma: A comprehensive analysis**

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**Abstract: Introduction:** Hodgkin lymphoma (HL) is a highly curable malignancy. Different pathological subtypes of classic Hodgkin lymphoma (CHL) are all treated with the same multimodality treatment, although they all do not have the same outcome. Our aim in this retrospective study was to highlight the presentation and prognosis of lymphocyte-depleted subtype and to compare it with the rest of subtypes in childhood CHL. **Patients and methods**: The data of 1197 children with biopsy-proven Hodgkin's lymphoma diagnosed from 2007 till 2017 at children cancer hospital Egypt were revised retrospectively. The outcome of different pathological subtypes are compared with other subtypes. **Results:** From a total of 1197 children with HL, ten patients (0.835%) were diagnosed as Lymphocyte Depleted Classic Hodgkin´s Lymphoma (LDCHL). All patients with LDCHL were diagnosed as high risk or advanced stages (3B, 4A, or 4B). Patients presented more often with advanced (high risk) disease as compared to other subtypes (100% versus 29.7%, respectively) and B symptoms (70% versus 32.3%, respectively). Risk factors as large mediastinal mass (50% versus 19%, respectively), high ESR (5 Out of 6 had elevated ESR), and involvement of more than three lymph nodes (80%). LDCHL cases showed an involvement of bone marrow in 22% of cases. The 5 years overall (OS) and Event-free survival (EFS) for LDCHL is the worst as compared to other pathologic subtypes CHL, 68.57% and 48% respectively. **Conclusion**: Children with LDCHL had a much aggressive presentation, responds inadequately to standard therapy, as well as having the worst outcome of all pathological subtypes CHL. Our results denote that children with LDCHL should receive more intensive chemotherapy.

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**1. Introduction:**

Hodgkin lymphoma (HL) is a highly curable, salvageable malignancy, approximately 90-95% can be cured that prompted the attention to use treatment program based on risk-adapted or response adapted to decrease long term morbidities for these patients 1. Hodgkin lymphoma (HL) is a B-cell malignancy, the pathology of HL is complex and variable2**.** In1994, the Revised European-American Lymphoma (REAL) classification separated the subtype nodular lymphocyte predominant HL (NLPHL) from CHL subtypes as different entity3**,** which had different prognosis, treatment regimen and outcome. CHL subtypes included, Nodular sclerosis (NS), mixed cellularity (MC), Lymphocyte depleted (LD) and lymphocyte-rich (LR). This new classification was approved by the World Health Organization (WHO) 2001**4, 5.**

Lymphocyte-depleted classical Hodgkin’s lymphoma is a rare entity, representing about 1% of all patients with newly diagnosed Hodgkin lymphoma**5.** Because of its rarity, little is known about clinical characteristics, course, prognosis, and treatment outcome. Histologically, there are two LD subtypes, the first one characterized by diffuse fibrosis with manyreed-sternberg cells and histiocytes with few lymphocytein a hypocellular background showing fibrosis, but, the second one is a reticular variant**,** showing abundant reed-sternberg cells with bizarre cytologic features. Exact diagnosis requires immune-histochemical staining, which aims to differentiate LDCHL from other HL and non-HL (NHL) subtypes 6, 7**.**

There was no large studies of children with LDCHL analyzed thus far, because numbers were too small for reliable conclusions and pediatric studies that explored clinical features as multivariate factors were limited by sample size and heterogeneity of treatments 8**.** To shed more light on the clinical course and treatment outcome for this rare entity of patients with LDCHL, we revisited our database to analyze the patient’s characteristics and treatment outcome.

**2. Patients and Methodology:**

This is a retrospective study including all patients under age of 18 years initially diagnosed as Hodgkin lymphoma and treated at children cancer hospital Egypt from July 2007 to July 2017. All patients were treated with ABVD (Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine) which was approved by the ethics committee from4-8 cycles and involved field radiotherapy (RT) based on their risk stratification. ABVD: adriamycin 25 mg/m2, bleomycin 10 mg/m2, vincristine 1.5 mg/m2, dacarbazine 375 mg/m2) was given twice monthly to all patients from4-8 cycles based on their risk stratification with a risk-stratified involved field radiation therapy given afterward regardless of the response. All patients underwent a staging PET scan before treatment and interim PET (post 2nd cycle of chemotherapy) ± post-treatment PET. Patients were classified into three risk stratifications, and staging was defined according to Ann Arbor staging 9, low risk (LR) included stages IA, IIA without bulky disease, intermediate risk (IR) included stages IA, IIA with bulky disease or stages IB, IIB IIIA and high risk (HR) included stages IIIB and IV. B symptoms (B) considered positive if the patient had at least one of the following, (1) unexplained fever above 38.0°C orally, (2) unexplained weight loss of 10% within the last six months preceding diagnosis, (3) drenching night sweats, (A) means no B symptoms. The bulky mediastinal disease was defined when the maximum diameter of the mediastinal lymph node to the maximal transverse diameter of the rib cage on an upright chest radiograph higher than 33 %, and bulky peripheral lymph node defined as greater than 6 cm, with aggregates measured transversely. An informed consent was taken from all patients or their guardians before starting treatment which was based on institutional review board guidelines. Histopathologic diagnosis was made initially by our pathologist if needed a revision of pathology was sent for central pathology review to the National Cancer Institute (NCI) -Egypt, expert pathology panel. Diagnostic criteria for. PET/CT and bone marrow biopsy assessed the extent of disease.

**Statistics:**

Differences between histologic subtypes in the distribution of demographic and clinical variables were assessed using the 2 test or Fisher’s exact test for dichotomous variables. Event-free survival (EFS) and overall survival (OS) were estimated according to the Kaplan-Meier method and compared between groups using the log-rank test. All reported Pvalues are two-sided. All variables results with a P value <0.05 were considered significant. EFS was calculated from the date of complete remission until progression, relapse, or death from any cause, and was considered censored at the date of last information on tumor status. OS was defined from the date of diagnosis until death as a result of any cause and was considered censored at the date of last information.

**3. Results:**

From a total of 1197 evaluable children diagnosed at children cancer hospital Egypt from July 2007 to July 2017 with biopsy-proven HL, included in this analysis, ten patients (0.835%) were diagnosed as Lymphocyte Depleted Classic Hodgkin Lymphoma and the rest of patients, other HL histology were identified. The median age was 14.5 years (10.7-17.8 years) with equal gender distribution. We compared clinical, pathological and outcome data between patients with LDCHL and patients with other types of HL. LDCHL showed a more progressive disease stage or advanced stages (3B, 4A, or 4B) than other types of CHL, advanced (high risk) disease (100% versus 29.7%, respectively) and more frequent B symptoms (70% versus 32.3%, respectively). Certain risk factors occurred more frequently in patients with LDCHL than in patients with other HL subtypes, such as large mediastinal mass (50% versus 19%, respectively), high ESR (5 Out of 6 had high ESR, 4 patients had no ESR results), and involvement of three or more lymph node areas (80%). Patients with LDCHL also had slow early response to treatment as interim PET CT (post 2nd cycle ABVD), which is the most important prognostic factor was positive in 5 out of 9(55.5%) patients. In addition, patients with LDCHL more often presented with an involvement of bone marrow (22%) as compared with other patients.

In total, 3.9% of all patients (n = 47) died, 40 % (4/10) of patients with LDCHL, 3.32 % (21/ 633) with NS, and 4.49 % (20/445) with MC and 3.8(1/6) with lymphocyte-rich HL Died at the end of the study, no deaths within the inter-follicular and NLPHL subtypes.

Patients with LDCHL showed a significantly inferior EFS (Figure 2) compared with all patients with other histologic subtypes 48% (95% CI, 24.58-93.75), patients with NS 87.23% (95% CI, 84.16-90.42) patients with MC subtypes 87.47% (95% CI, 83.89-91.2), and for patients with lymphocyte-rich 84.28% (95% CI, 71.25-99.7). It was noted that LDCHL carries the worst outcome (Table 4).

Inferiority was also observed for OS of patients with LDCHL compared with non-LDCHL (Figure 1) or compared with NS or MC histology. Five-year OS rates were 68,57% for LDCHL (95% CI, 44.47-100), 96.43% for NS (95% CI, 94.64-98.25), and 95.68% for MC (95% CI, 93.60-97.81), 96.15% for LR (95% CI, 89.04-100) (Table 3).

**Table (1): Characteristics of Patients with Lymphocyte Depleted subtype Hodgkin Lymphoma**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient No.** | **Age** | **Stage at presentation** | **Risk at presentation** | **Gender** | **Initial Bone Marrow Biopsy** | **Initial Bone Marrow Aspirate** | **The result of Interim PET-CT** | **Mediastinal** | **More than 3 LN** | **LDH** | **ESR** | **Status** |
| **#1** | **10.7** | **3B** | **HR** | **Male** | **Not Done** | **Not Done** | **Not Done** | **No** | **No** | **Not Found** | **Not found** | **Alive** |
| **#2** | **15.4** | **3B** | **HR** | **Female** | **Negative** | **Negative** | **Positive** | **Yes** | **Yes** | **Not Found** | **Not found** | **Dead** |
| **#3** | **12.9** | **3B** | **HR** | **Male** | **Negative** | **Negative** | **Negative** | **Yes** | **Yes** | **Not Found** | **Not found** | **Dead** |
| **#4** | **16.2** | **4A** | **HR** | **Female** | **Negative** | **Negative** | **Positive** | **Yes** | **Yes** | **Not Found** | **Not Found** | **Dead** |
| **#5** | **16.2** | **4A** | **HR** | **Female** | **Negative** | **Negative** | **Positive** | **Yes** | **Yes** | **471** | **97** | **Alive** |
| **#6** | **17.8** | **4B** | **HR** | **Male** | **Negative** | **Negative** | **Negative** | **No** | **Yes** | **559** | **87** | **Alive** |
| **#7** | **13.6** | **4B** | **HR** | **Male** | **Positive** | **Positive** | **Positive** | **No** | **Yes** | **805** | **65** | **Lost Follow Up** |
| **#8** | **13.4** | **4B** | **HR** | **Female** | **Positive** | **Positive** | **Negative** | **No** | **Yes** | **1100** | **100** | **Alive** |
| **#9** | **11.1** | **4A** | **HR** | **Female** | **Negative** | **Negative** | **Negative** | **No** | **No** | **378** | **12** | **Alive** |
| **#10** | **16.2** | **4B** | **HR** | **Male** | **Negative** | **Negative** | **Positive** | **Yes** | **Yes** | **1028** | **62** | **Dead** |

**Table (2): Number and % of deaths related to each pathological subtype**

|  |  |  |
| --- | --- | --- |
| Pathology | Cases=1197 | Number of Deaths |
| Lymphocyte Depleted CHL | 10 = 0.8 | 4 = 40% |
| Mixed Cellularity CHL | 445 = 37.2% | 20 = 4.49% |
| Nodular Lymphocyte Rich CHL  Nodular Lymphocyte Predominant  Interfollicular | 26 = 2.2%  52 = 4.3%  16 = 1.3% | 1 = 3.8%  --------  ---------- |
| Nodular Sclerosis CHL | 633 = 52.9% | 21 = 3.32% |
| NOS | 15 = 1.3% | 1 = 6.66% |

**Table (3): Overall survival of subtypes**

|  |  |  |
| --- | --- | --- |
| Pathology | Overall Survival | 95% Confidence Interval |
| Lymphocyte Depleted cHL | 68.57% | (44.47-100) |
| Mixed Cellularity cHL | 95.68% | (93.60-97.81) |
| Nodular Lymphocyte Rich | 96.15% | (89.04-100) |
| Nodular Sclerosis cHL | 96.43% | (94.64-98.25) |
| NOS | 87.50% | (67.34-100) |

**Table (4): Event Free Survival according to pathology subtypes with 95% C. I**

|  |  |  |
| --- | --- | --- |
| Pathology | Event-free Survival | Interval |
| Lymphocyte Depleted CHL | 48% | (24.58-93.75) |
| Mixed Cellularity CHL | 87.47% | (83.89-91.2) |
| Nodular Lymphocyte Rich CHL | 84.28% | (71.25-99.7) |
| Nodular Sclerosis CHL | 87.23% | (84.16-90.42) |
| NOS | 53.62% | (31.86-90.27) |

**Table (5): Number of cases and events for each pathological subtypes.**

|  |  |  |
| --- | --- | --- |
| Pathology | Number of cases | No of events |
| Lymphocyte Depleted CHL | 10 | 5 = 50% |
| Mixed Cellularity CHL | 445 | 45 = 10 % |
| Nodular Lymphocyte Rich CHL | 26 | 6 = 23% |
| Nodular Sclerosis CHL | 633 | 71 = 11% |
| NOS | 15 | 6 = 40% |

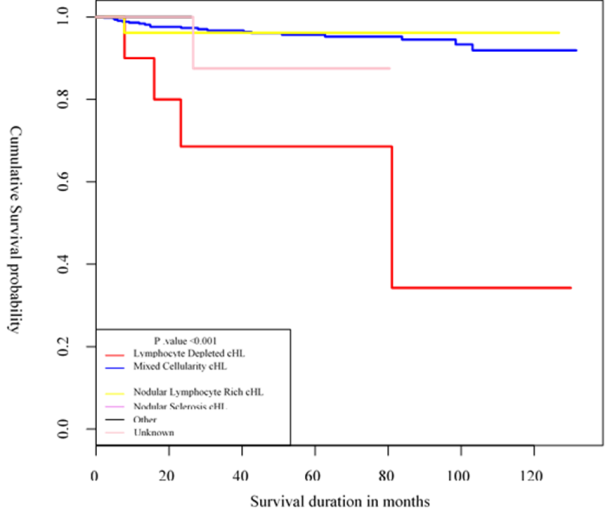
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Figure (1) Overall Survival of Hodgkin Lymphoma Patients by Pathology

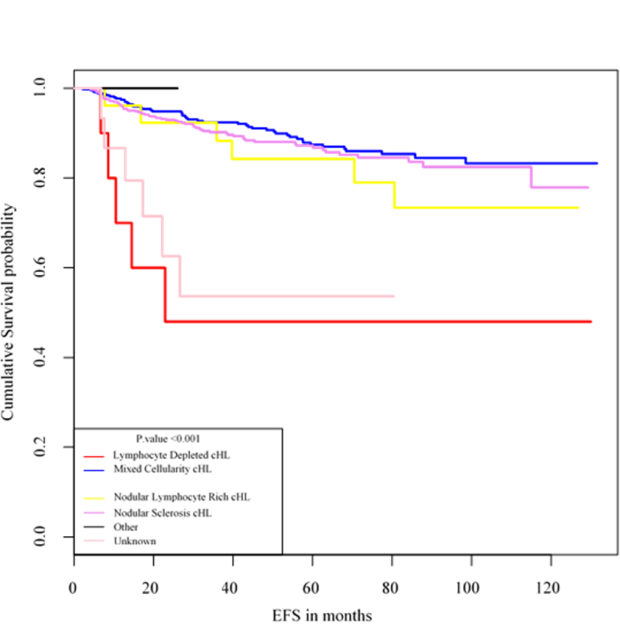
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Figure (2) Event Free Survival according to pathology

Events included refractory or progressive disease, relapse, death, and second malignancy, out of 1179 patients, eight patients did not achieve an initial remission with front-line therapy, three patients developed second malignancy in the form of thyroid carcinoma in one patient, Non-Hodgkin lymphoma in the second patient and acute myeloid leukemia in the last one, relapse occurred in 120 patients, total number of deaths were 47 patients (37 within relapsed patients, 4 patients within progressive or refractory group and 6 patients died in first complete remission). It was shown that the number of events were highest in the LDCHL group 50%, relapse occurred in three patients in the first years off-treatment, and two patients did not achieve remission to first-line chemotherapy (Table 5), Four patients received 2nd line ICE (Ifosfamide, Carbopltin and Etoposide) and one patient received gemcitabine and vinorelbine followed by RICE (Rituximab, Ifosfamide, and Etoposide) as the pathology showed a shift in the histology to primary mediastinal B cell lymphoma, two patient underwent autologous bone marrow transplantation (BMT).

Four patients alive in complete remission after the first line, one patient alive in complete remission after salvage chemotherapy and BMT, deaths occurred in 4 patients (3 patients died with the disease, one patient died with infection) and one patient lost follow up.

**4. Discussion**

There are limited reports addressing the outcome and impact of pathological subtypes in pediatric patients with HL as most published results focusing on the outcome in adult patients. Many of these reports have treated different subgroups with the same regimen.

The aim of our study was to describe the clinical characteristics of LDCHL in pediatric patients with HL and to determine treatment outcome for this rare entity which accounting for 0.835% of all our HL patients and has the worst outcome. In general, the outcome of the few numbers of patients with LDCHL histology who were analyzed in the previous studies or included in clinical trials, seem to be the worst as compared to patients with other histologic HL subtypes 10.

We analyzed 1197pediatric patients with classic HL presented to our hospital, from 2007 till 2017, for children less than 18 years of age, patients with LD histology presented more often with unfavorable characteristics and risk factors as compared with patients with non-LD HL, they presented more often with advanced stage (high risk) disease (100% versus29.7%, respectively) and B symptoms (70% versus32.3%, respectively), large mediastinal mass (50% versus19%, respectively), high ESR (5 Out of 6 had elevated ESR), and involvement of more than three lymph node areas (80%). In addition newly diagnosed patients showed more often an involvement of bone marrow (22%) table (1).

These findings coincides with Klimm et al, 2011 who reported that patients with LD histology, compared with patients with non-LD HL, presented more with advanced disease (74% versus42%, respectively; P <.001), B symptoms (76% versus 41%, respectively; P <.001), large bulky mediastinal mass (32% versus 19%, respectively; P <.0046), extranodal involvement (25% versus 14%, respectively; P<.0011), high ESR (76% versus 47%, respectively; P <.001), involvement of three or more lymph node areas (88% versus 60%, respectively; P <.001) and involvement of bone marrow (11% versus 4%, respectively; P <.0098) and liver (19% versus 4%, respectively; P<.001)8**.**

In our study children less than 18 years of age with LDCHL, compared with patients with other HL histologic subtypes, had significantly the lowest OS of all subtypes 68.57% and the lowest EFS 48% (Table 3,4), with poorer rate of complete remission and inadequate response, 5/9 (55.5%) had slow early response with positive interim PET CT post 2nd cycle ABVD and 20% (2/10) had primary progressive disease. This is comparable to the German Hodgkin study group report which stated that LDCHL compared with patients with other HL subtypes had (PFS, 71% versus 85%, respectively; P <.001; OS, 83% versus 92%, respectively; P =.0018)8**.**

The histologic diagnosis of LDHL is often is complex and not straight-forward, and its distinction and differentiation from aggressive non- Hodgkin’s lymphomas (NHL) can be difficult, Slack et al.2009 reported that expert pathologists can distinguish LDCHL from other entities including, anaplastic large cell lymphoma, diffuse large B cell lymphoma or gray zone lymphoma by means of morphology, immune-phenotyping, and molecular genetic analyses 7**.** In one report, this led up to 22% of all patients with HL being originally classified as LDCHL, and after revision of pathology, it revealed that 10 patients had NHL, 13 patients NS, 7 patients other subtypes of CHL and only 9 patients had LD, they also reported that, the outcome of LD was the same as others CHL subtypes and the worse outcome for LD may be due to inclusion of high grade NHL into this subtype so diagnosis of LD should be made cautiously especially with unusual features 11, 12. We had one patient developed recurrence and lymph node biopsy showed that he had primary mediastinal B cell lymphoma, we did not know if this patient was misdiagnosed initially or there was a shift in the pathology at time of relapse, so expert well-trained pathologists with an adequate revision of diagnosis are required to distinguish LDCHL from other entities of aggressive NHL.

It was observed that there is ongoing increase in the incidence of subtype called NOS (not otherwise specified, this subtype defined a patient with CHL without further histologic subtyping13, This increasing rate may reflect changes in diagnostic practice like, smaller biopsies that making precise accurate diagnoses is difficult, pathologists sometimes relied heavily on CHL as the terminal category during histologic classification. leading to incorporation of patients that previously would have been classified as more specific histologic subtypes. In our study this group constitute 1.3% of our population with lower EFS and OS 53.62% (95% CI, 31.86-90.27) and OS 87.50% (95% CI 67.34-100), we need to highlight insights into diagnostic and classification practices for NOS as the decreasing ability to diagnose MC and LD led to greater use of the NOS classification.

In our study the OS and EFS for patients with LDCHL was 68.57% and the EFS 48%, this was consider lower than other German Hodgkin study group who reported that the PFS and OS was 71% and 83% respectively for patients with LDCHL8**.** They use in their regimenbleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) for advanced stage, that may reflect that intensive chemothepy regimen may be needed for this group and may improve the outcome.

Current multimodality treatment protocols that achieve better tumor control might have blunted the effect of histology and other risk factors on outcome. In contrast, results from previous studies suggest that histologic groups continue to have an important prognostic significance, even in the recent combined modality treatment era, with a significantly worst prognosis of LD subtype,14this was in agreement with our results as we adopted multimodality treatment with intensive chemotherapy and involved field radiation to all patients irrespective to response and still patients with LDCHL had the lowest OS of all subtypes 68.57% and the lowest EFS 48%, with higher percentage of inadequate response and progressive disease, so histologic subtypes still considered prognostic significance and this group of patients (LDCHL) still need dose-intense treatment strategies. All our patients presented with advanced disease (100%) so we cannot conclude if the outcome of these patients may be better according to the stage of disease and other favorable prognostic factors.

Finally, although HL histologic subtypes are not included in clinical decision-making or in the risk stratification criteria, their varying survival patterns suggest that more tailored therapies might be reconsidered 15,16. Accurate histologic subtyping diagnosis is needed, which requires the use of excisional biopsies as indicated and comprehensive central registry quality control. Less invasive biopsy techniques have patient benefits, and should be used in limited case, for deep lesions, or when an open biopsy is clinically contraindicated by comorbidity. However, in other situations, excisional biopsies should be used as the first choice for the initial diagnosis, in accordance with National Comprehensive Cancer Network guidelines (NCCN)17.

HL histologic subtypes show considerable epidemiologic variation 18, 19. The uniform decline in the less common subtype like LD, the absence of trends in rates including this subtype, support the need for cooperative study groups to collaborate together for better diagnosis.

We conclude from this analysis that patients with LDCHL had a much aggressive presentation, responds inadequately to standard therapy, as well as having the worst outcome of all pathological subtypes CHL. Our results denote that children with LDCHL had a decimal outcome. They should receive an intensive chemotherapy may be more than other subtypes, as our series of children with LDCHL may be the first (in this age category) to identify differences in disease characteristics, prognostic factors, and treatment outcomes between pediatric patients with LDCHL in comparison to other CHL entities as most published results in adults.

A collaborative effort between international centers dealing with childhood HL should take place to properly identify this category of patients as its paucity (0.8-1%) makes it difficult to conclude a decision about the optimum best approach to deal with this subtype of CHL. Integration of molecular and cytogenetic studies as well as biological markers might be useful in further identifying those patients.

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