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Pediatric Hodgkin Lymphoma Overview in Albania during the Last Decade

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Abstract

Background: Hodgkin lymphoma (HL) is a rare malignancy characterized by a malignant proliferation of cells in the reticuloendothelial system, mainly lymph node, and the presence of Reed-Sternberg cells with a relatively good prognosis compared to other pediatric malignancies. This study aimed to produce epidemiologic and clinical data on HL for Albania, aiming for a better understanding of the disease presentation to diagnose it at an earlier stage with the result of a better outcome.

Methods and Results: This single-center, retrospective study performed in the Mother Theresa University Hospital Center (Tirana, Albania) analyzed epidemiological and clinical data of pediatric patients under 14 years of age diagnosed with HL during a 10-year study period from 2012 to 2022. During the last 10 years, 25 children (ages 0-14) were diagnosed with HL at UHC "Mother Theresa," Tirana. From the demographic data of our study, most patients (68%) were in the age group of 10-14. The male-to-female ratio was 2.12:1. The first clinical presentation was mainly because of lymphadenopathy in 92% of patients, with the presence of B symptoms in 68%. In most cases, the CBC was not affected, yet 24% of patients had high platelets, and 12% had low RBCs, while WBCs increased in 16% of patients and decreased in 12%. Lymphopenia and monocytosis were found in more than half of cases. Around 68% of patients had high levels of LDH and CRP. ESR and ALP were high in 64% of patients, Ferritin was high in 32%, and fibrinogen level was high in 28%. According to the Ann Arbor system, most of our patients were at stage II (32%), followed closely by stage I (28%) and stage III (24%), and only 16% were at stage IV upon presentation. The most common histopathologic type was nodular sclerosis classical HL, presented in 44% of cases.

Conclusion: HL is a relatively frequent pediatric malignancy in young adults, affecting mainly males, and is diagnosed at a relatively early stage in our country.**(International Journal of Biomedicine. 2024;14(1):26-29.)**

Keywords: pediatric Hodgkin lymphoma • lymph node • complete blood count • diagnosis

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Abbreviations

CBC, complete blood count; **HL**, Hodgkin lymphoma; **LN**, lymph node; **LRCHL**, lymphocyte-rich classic HL; **LDCHL**, lymphocyte-depleted classical HL; **MCCHL**, mixed cellularity classical HL; **NSCHL**, nodular sclerosis classical HL; **NLPHL**, nodular lymphocyte-predominant HL.

Introduction

Hodgkin lymphoma (HL) is a rare malignancy characterized by a malignant proliferation of cells in the reticuloendothelial system, mainly lymph node (LNs), and the presence of Reed-Sternberg cells with a relatively good prognosis compared to other pediatric malignancies.[1] There are several risk factors, but the strongest until now are the family history of previous lymphoma or adenopathy and previous Epstein-Barr virus infection.[2]

According to histological features, two main variants of Hodgkin's Lymphoma are classic HL in 95% of cases and nodular lymphocyte-predominant HL (NLPHL) in 5%. Classic HL is divided into four subtypes: nodular sclerosis classical

HL (NSCHL), mixed cellularity classical HL (MCCHL), lymphocyte-rich classic HL (LRCHL), and lymphocyte-depleted classical HL (LDCHL).[1,3] It is mainly presented with superficial lymphadenopathy with or without B symptoms, which, if diagnosed in an early stage, has a very good survival rate of over 90% in developed countries.[1,2]

Unfavorable prognostic factors of pediatric HL include age between 5 and 10, male gender, stage IV disease (the Ann Arbor staging system), presence of bulky disease and B symptoms at presentation, a hemoglobin level <10.5 g/dL, WBC>15×10³/μL, lymphocyte count <600×10³/μL, a serum albumin level <3.5g/dL.[1,4]

Materials and Methods

This study aimed to produce epidemiologic and clinical data on HL for Albania, aiming for a better understanding of the disease presentation to diagnose it at an earlier stage with the result of a better outcome. This single-center, retrospective study performed in the Mother Theresa University Hospital Center (Tirana, Albania) analyzed epidemiological and clinical data of pediatric patients under 14 years of age diagnosed with HL during a 10-year study period from 2012 to 2022. Data were extracted from charts. A positive diagnosis of HL was considered only if confirmed by a biopsy sample histopathologic examination. This is a retrospective descriptive study where patient identity and sensitive information are not revealed, even though the parents have signed the hospital-informed form on scientific data usage. Since this is not an interventional study, ethics approval was not recommended.

Results

During the last 10 years, 25 children (ages 0-14) were diagnosed with HL at UHC "Mother Theresa," Tirana. From the demographic data of our study, most patients (68%) were in the age group of 10-14, followed by the age group of 5-9 (28%). HL is rare in children under 5; in our study, only one patient was diagnosed under 5. Age distribution is presented graphically. The male-to-female ratio was 2.125:1, and all males were in the age group of 1-9. Regarding geographic distribution, most of the patients lived in central Albania (28% from Tirana County, 16% from Elbasan County, 16% form Dibra County), as more than half of the population is concentrated in this region.

From clinical data, we found that the first clinical presentation was mainly because of lymphadenopathy in 92% of patients, with the presence of B symptoms in 68%. Table 1 presents the frequency of encountering each symptom and other common clinical findings on physical examination. Hepatosplenomegaly was present in 40% of patients, and cough and dyspnea in 44% and 32%.

The most common site of LN involvement was the cervical region, found in up to 91% of patients, followed by the supraclavicular region in 69%. Meanwhile, the axillar and inguinal regions were each affected in 44% of all cases. Affected nodes were mostly not painful, often found bilaterally in 83%, mobile locally in 78% of cases, and with a firm consistency in 78% of cases. Most patients had a package of LNs affected, rather than just one (74%).

Table 1.

The frequency of encountering each symptom and other common clinical findings on physical examination.

Clinical Finding	Number of cases	%
B symptoms	17	68%
Peripheral lymphadenopathy	23	92%
Hepatosplenomegaly	10	40%
Cough	11	44%
Dyspnea	8	32%
Malaise	12	48%
Abnormal breath sounds	16	64%
History of antibiotic intake	21	84%

Important diagnostic information was also extracted from the laboratory investigations. In most cases, the CBC was not affected, yet 24% of patients had high platelets, and 12% had low RBCs, while WBCs increased in 16% of patients and decreased in 12%. A leukocyte count >15×10³/μL is an unfavorable prognostic factor,[4] and in our study, two patients had leukocytosis, with 80% of all having left formula shift with increased bands. Lymphopenia and monocytosis were found in more than half of cases. Hemoglobin <10.5 g/dL is another unfavorable prognostic factor,[4] but most of the patients had a hemoglobin level >11.5 g/dL, and only 32% had a hemoglobin level <10.5g/dL. The median neutrophil count of our patients was 5.4×10³/μL while the median lymphocyte count was 1.7×10³/μL, giving the value of the neutrophil/lymphocyte ratio of 3.17.

Other inflammatory markers like ESR, CRP, ferritin, fibrinogen, LDH, ALP, and albumin were also studied (Chart 1). Around 68% of patients had high levels of LDH and CRP from the initial laboratory tests. ESR and ALP were high in 64% of patients, Ferritin was high in 32%, and fibrinogen level was high in 28%. Albumin is another parameter with a predictive value considered unfavorable if lower than 3.5g/dL,[4] and such levels were encountered in only 20% of our patients.

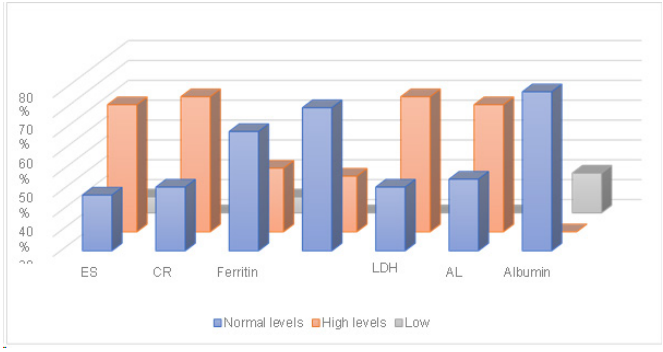

Chart 1. *Inflammatory markers levels on initial tests on patients diagnosed with HL*

We analyzed the presence of bulky disease that was also considered a bad prognostic factor[4] in the following cases: a mediastinal mass with a maximum width equal to or greater than one-third of the internal transverse diameter of the thorax at any level on a chest X-ray or a nodal mass of more than 6 cm diameter.[1,5] In our study, bulky disease was observed in 32% of cases, and 5 out of 8 patients had a mediastinal mass.

CT scan revealed even more affected LN sites than the physical examination. However, the most affected sites were still the cervical regions (76%), and 64% of patients had affected mediastinal nodes. Submandibular and occipital regions were rarely affected.

The liver and spleen are two other frequently affected organs, and they were found enlarged in 40% of patients through physical examination and in 88% through abdominal ultrasound.

Evaluation of metastasis is very important in staging HL. In our study, the metastatic sites were as follows: 41% of patients had splenic metastasis, 23% had lung metastasis, followed by liver metastasis in 12% of patients, and very rarely (in 4 patients) metastasis was observed in the peritoneum, mesentery, bone (right pelvis) and adrenal gland.

After all the investigations, patients were staged at presentation based on the Ann Arbor system. Most of our patients were at stage II (32%), followed closely by stage I (28%) and stage III (24%), and only 16% were at stage IV upon presentation.

In this cohort, we also studied histopathology characteristics. The most common histopathologic type was NSCHL, presented in 44% of cases. The second most frequent was MCCHL in 32% of patients. The LRCHL type was present in 12% of patients, while the LDCHL was present in only 4%. NLPHL was observed in 8% of patients (Chart 2).

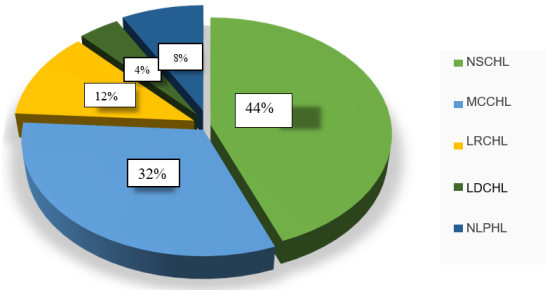

Chart 2. *Distribution of patients according to the histological HL subtypes*

Discussion

This study has the advantage of being realized in a single country center, giving us a good national HL overview. From the data, we calculated an incidence of 6-7 cases/year/million children up to 14 years of age, even though we are not very accurate since several cases are lost from the system because patients left to continue treatment abroad before coming to our center. The age and gender distributions are like those of other worldwide studies, where males under 15 have a higher incidence of HL than females.[1,6-8]

The most common clinical presenting symptom in pediatric patients is peripheral lymphadenopathy, but most superficial enlarged LNs in children are benign; therefore, physicians should search for other indicators that would lead the diagnosis towards malignity, like persistence of lymphadenopathy more than 6 weeks, the presence of constitutional B symptoms, the imagining characteristic of these LNs and unresponsiveness to a course of antibiotics. In our study, B symptoms were also observed frequently, in around 68% of cases, which is higher than what is expected from international studies. Probably being a retrospective study, this is overestimated and considered positive for any case of mild fever, weight loss, or sweating.[8]

As for the lab test, no specific investigations besides histopathology can differentiate a benign from malignant LN, but several persistent blood changes and inflammatory markers indicate an underlying malignant process or a bed prognosis. Present in about one-third of our cohort were a high leukocyte count with neutrophil/lymphocyte ratio >3, hemoglobin <10.5g/dL, a high CRP, ESR, ferritin, or fibrinogen, and a low albumin level. These are predictors of harmful diseases.[4,9]

Imaging increases the chances of finding affected LNs and distant metastasis, especially to the spleen and lung that are the commonest, since it is much more sensitive and, for instance, scaled up the Ann Arbor staging.

In our study, around 92% of patients had classic HL, and only 8% were nodular lymphocyte-predominant HL, like the international statistics. We want to mention two atypical presentations of HL. First, a 13-year-old female patient referred only to hip pain, localized in her right pelvis. She had high levels of inflammatory markers and normal CBC. The CT scan revealed multiple bone lesions in her pelvis as well as on her inguinal LNs. Biopsy revealed HL on her LNs and osteoma on her bone. At this point, it was difficult to evaluate which malignant process had started first. After multiple discussions and other studies, such as immunophenotyping, it was concluded that the patient had primary HL of the bone. We were able to find other similar cases published.[10] Luckily, this is considered the first stage, according to the Ann Arbor staging system, and has generally a good prognosis. It is important to note that a differential diagnosis with osteomyelitis, Ewing sarcoma, and osteosarcoma should be made in such cases.

Our second, a 4-year-old male patient, presented with idiopathic thrombocytopenic purpura and superficial adenopathy. A biopsy of the enlarged LN revealed HL. Our main dilemma was whether idiopathic thrombocytopenic purpura and HL coexisted independent of each other, or one brings the other. After researching this topic,[11,12] we concluded that these conditions were related. Our leading theory is that HL can cause a great deal of inflammation, triggering different autoimmune processes that lead to idiopathic thrombocytopenic purpura.

Conclusion

HL is a relatively frequent pediatric malignancy in young adults, affecting mainly males, and is diagnosed at a relatively early stage in our country. Most pediatric HL patients present with persistent enlarged LNs that do not resolve with an antibiotic course. Other organs affected or the presence of B symptoms, such as hepatosplenomegaly and persistent inflammatory changes in laboratory tests, should not be dismissed. Paying attention to each of the findings that indicate a malignancy will enable early detection and treatment with the result of a better prognosis.

Competing Interests

The authors declare that they have no competing interests.

References

1. Takahara T, Satou A, Tsuzuki T, Nakamura S. Hodgkin Lymphoma: Biology and Differential Diagnostic Problem. Diagnostics (Basel). 2022 Jun 20;12(6):1507. doi: 10.3390/diagnostics12061507. PMID: 35741318; PMCID: PMC9221773.
2. Massini G, Siemer D, Hohaus S. EBV in Hodgkin Lymphoma. Mediterr J Hematol Infect Dis. 2009 Nov 24;1(2):e2009013. doi: 10.4084/MJHID.2009.013. PMID: 21416003; PMCID: PMC3033177.
3. Mani H, Jaffe ES. Hodgkin lymphoma: an update on its biology with new insights into classification. Clin Lymphoma Myeloma. 2009 Jun;9(3):206-16. doi: 10.3816/CLM.2009.n.042. PMID: 19525189; PMCID: PMC2806063.
4. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med. 1998 Nov 19;339(21):1506-14. doi: 10.1056/NEJM199811193392104. PMID: 9819449.
5. ASH-SAP. American Society of Hematology Self-Assessment Program, Seventh Edition. Edited by Adam Cuker, Jessica K. Altman, Aaron T. Gerds, Ted Wun. American Society of Hematology, 2019.
6. Zhou L, Deng Y, Li N, Zheng Y, Tian T, Zhai Z, Yang S, Hao Q, Wu Y, Song D, Zhang D, Lyu J, Dai Z. Global, regional, and national burden of Hodgkin lymphoma from 1990 to 2017: estimates from the 2017 Global Burden of Disease study. J Hematol Oncol. 2019 Oct 22;12(1):107. doi: 10.1186/s13045-019-0799-1. PMID: 31640759; PMCID: PMC6805485.
7. Shamoon RP, Ali MD, Shabila NP. Overview and outcome of Hodgkin's Lymphoma: Experience of a single developing country's oncology centre. PLoS One. 2018 Apr 12;13(4):e0195629. doi: 10.1371/journal.pone.0195629. PMID: 29649329; PMCID: PMC5896958.
8. PDQ Pediatric Treatment Editorial Board. Childhood Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. 2023 Dec 18. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002–. PMID: 26389170
9. Kaplama ME, Güneş AK, Erden B. Evaluation of the predictive role of neutrophil/lymphocyte ratio in the diagnosis of lymphoma in patients with asymptomatic and ısolated cervical lymphadenopathy. Braz J Otorhinolaryngol. 2021 Mar-Apr;87(2):210-216. doi: 10.1016/j.bjorl.2020.06.012. Epub 2020 Aug 1. PMID: 32798200; PMCID: PMC9422533.
10. Siddiqui DE, Akbar HF, Sadiq H, Iftikhar N, Khan MR, Raza MR. Primary Hodgkin's Lymphoma of bone in 7-year-old- an exceptional case report of youngest child in literature. Cancer Treat Res Commun. 2021;29:100448. doi: 10.1016/j.ctarc.2021.100448. Epub 2021 Aug 19. PMID: 34488186.
11. Kristinsson SY, Landgren O, Sjöberg J, Turesson I, Björkholm M, Goldin LR. Autoimmunity and risk for Hodgkin's lymphoma by subtype. Haematologica. 2009 Oct;94(10):1468-9. doi: 10.3324/haematol.2009.010512. PMID: 19794095; PMCID: PMC2754970.
12. Tomlinson R, Yaxley J. Thrombotic thrombocytopenic purpura associated with Hodgkin lymphoma and non-Hodgkin lymphoma. Pathology. 2018 Dec;50(7):776-777. doi: 10.1016/j.pathol.2018.05.011. Epub 2018 Oct 9. PMID: 30314645.

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