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Prevalence of Common Non-Hodgkin Lymphomas and Subtypes of Hodgkin Lymphoma by Nodal Site of Involvement

A Systematic Retrospective Review of 938 Cases

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Abstract: Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) represent a heterogeneous group of malignant lymphoid tumors, which have distinct histological and/or biological characteristics with preferential nodal involvement. However, none of the previous studies have assessed the prevalence of common NHL and HL subtypes at each nodal site of involvement.

The aim of our study was to determine the prevalence of HL and NHL subtypes depending on their nodal sites of involvement.

We conducted a single-center retrospective study of 938 lymphoma cases diagnosed in the Pathology Department of Toulouse Purpan Hospital in France between 2001 and 2008, taking into account the site that corresponded to the diagnostic biopsy.

The most frequent sites were cervical lymph nodes (36.8% of all cases), inguinal lymph nodes (16.4%), axillary lymph nodes (11.9%), and supraclavicular lymph nodes (11%). We found an unexpected association between intraparotid nodes and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and between inguinal nodes and follicular lymphoma. The risk of having classical Hodgkin lymphoma (CHL) was 15 times greater in patients with mediastinal lymphoma compared to those with other sites of involvement. Regarding HL, nodal and extranodal mediastinal sites and supraclavicular nodes were more likely to be involved by nodular sclerosis Hodgkin lymphoma (NSCHL). In addition, intra-abdominal lymph nodes were more frequently involved by lymphocyte depleted

Hodgkin lymphoma compared to inguinal nodes where NLPHL predominated.

Our study shows that some lymph node sites have a disproportionate prevalence of specific subtypes of lymphoma. Identifying these sites may aid to diagnose and better elucidate the pathogenesis of these tumors.

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Abbreviations: aOR = adjusted odds ratio, CHL = classical Hodgkin lymphoma, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, EBV = Epstein-Barr virus, FL = follicular lymphoma, HL = Hodgkin lymphoma, IC = confidence interval, NHL = non-Hodgkin lymphoma, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, NSCHL = nodular sclerosis Hodgkin lymphoma, TCL = T-cell lymphoma.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) represent a heterogeneous group of malignant lymphoid proliferations of extra medullary origin. This heterogeneity is associated with various clinical, pathological, immunological, and cytogenetic presentations, and thus the prognoses are quite variable.¹ The primary site of involvement of NHL and HL, however, is essentially nodal, and some NHLs and subtypes of HL may have preferential nodal sites of involvement. The anatomic distribution of HL has been previously studied and usually located in the lymph nodes of the neck and the mediastinum.² Furthermore, the commonest site of involvement was cervical region followed by axillary region.³⁻⁵ In a study including 500 malignant lymphomas,⁶ the authors found that the primary site of involvement for HL was in lymph nodes or the spleen in 99.5% of cases with prominent involvement in cervical and mediastinal areas, whereas so-called “lymphosarcomas” occurred mainly in axillary, iliac, and inguinal regions. These observations were confirmed in another study by Mauch et al.⁷ Interestingly, the authors found different patterns of presentation depending on the subtype of HL. Patients with the HL lymphocyte predominant (nodular lymphocyte predominant Hodgkin lymphoma [NLPHL]) subtype were less likely than patients with nodular sclerosis (NS) to have mediastinal involvement, and their main sites of involvement were cervical and inguinal. Few studies have analyzed the distribution of distinct NHL types. The time to diagnosis could be shortened by focusing on the most frequent lymphomas based on nodal site and patient characteristics. Moreover, because the most frequent sites of involvement are most likely the sites of origin for each lymphoma, this information may provide indirect clues for the pathogenesis and etiology of each type of lymphoma. The aim of this study was to assess the

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CL, GRP, SV, and PB collected and reviewed the cases. CL, CD, and PAG analyzed data. CD, CL, and PB designed and supervised the study. CL, CD, SV, and PB wrote the manuscript.

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prevalence of common NHLs and HLs subtypes at each nodal site of involvement. We selected lymph nodes or other sites used to make the diagnosis, because these are clinically relevant (revelation of the tumor) and are generally the largest found and thus likely to be located in one of the primary sites of the disease.

MATERIALS AND METHODS

Study Design

We conducted an observational, retrospective case study based on a single hospital.

Data Collection

We reviewed the medical records of all cases of primary NHL and HL diagnosed in the Pathology Department of Purpan Hospital, Toulouse, France, from January 2001 to June 2008. Classification was made according to the 4th edition of the World Health Organisation (WHO) classification of tumors of hematopoietic and lymphoid tissues.¹ In total, 1949 cases were reviewed using the following inclusion criteria: histologically documented primary diagnosis of any subtype of HL or of a common NHL (follicular lymphoma [FL], diffuse large B-cell lymphoma (DLBCL), T-cell rich DLBCL, Burkitt lymphoma (BL), mantle cell lymphoma, nodal marginal zone B-cell lymphoma, B-cell prolymphocytic lymphoma, anaplastic large B-cell lymphoma, chronic lymphocytic leukemia, lymphoplasmocytic lymphoma, angioimmunoblastic T-cell lymphoma (TCL), T-lymphoblastic lymphoma, and anaplastic large TCL; and the presence of at least 1 histologically documented nodal or mediastinal involvement. Cases with nodal involvement at an unspecified location were excluded. For cases with mediastinal involvement, we included the mediastinum as a site of involvement even when nodal involvement was not histologically certain because it is often difficult or impossible to distinguish between a nodal or adjacent tissue involvement (such as the thymus). There were 1105 cases with at least 1 nodal (1059) or mediastinal (56) site of involvement, and 167 cases were excluded from the study. Institutional ethical approval was obtained in compliance with the Helsinki protocol.

Sample Size

Because the aim of our study was primarily descriptive, we did not estimate a required sample size. However, based on the prevalence of NHL and HL in the general population, an a priori computation of the statistical power of our study was performed. The precision was estimated to be $\pm 5\%$ to 10% for the prevalence of common NHLs and HL subtypes in the most frequent nodal sites of involvement.

Documented Variables

For each case, demographic data (sex and age), diagnosis, Epstein-Barr virus (EBV) status (based on LMP1 immunostaining and/or EBER probe for HL cases), nodal involvement sites, number of nodal involvement sites, and presence of extranodal involvement sites were recorded. The nodal site of involvement was defined as the nodal site at the time of diagnosis that allowed the histological diagnosis. For the analysis, age was grouped into 3 classes: under 14-years old, between 15 and 59-years old, and above 60-years old. Indeed, NHL can affect any age group but mostly occurs in older patients. However, some NHLs (such as mediastinal B-cell

lymphoma) and HL also primarily affect younger adults and children.¹

Statistical Analysis

In our descriptive analysis, frequencies are presented as counts (n) and percentages (%), whereas quantitative variables are presented as arithmetic means (m) and standard deviations (SD). For each parameter, the 95% confidence interval (95% CI) was calculated. Prevalences were analyzed according to 2 perspectives: first, the prevalence of common NHLs and subtypes of HL by nodal involvement; second, the prevalence of nodal involvement sites by lymphoma. Univariate analyses were conducted to compare the prevalence of common NHLs and subtypes of HL by nodal involvement site using the chi-square test or Fisher exact test (when required). This association between nodal site and lymphoma subtypes was estimated using logistic regression, where the odds ratio (OR) was adjusted odds ratio (aOR) for sex and age. The uncorrected *P*-values are presented. Additionally, due to the large number of tested null hypotheses, *P*-value correction for multiple tests was performed using the Benjamini and Hochberg⁸⁻¹⁰ false discovery rate under general dependence for each site of involvement, where the false discovery rate was kept at 5%.

To assess the potential bias due to excluding data with unspecified locations, we compared the age, sex, and the prevalence of NHL and HL subtypes in the excluded group to the prevalence in our dataset.

Statistical significance was assessed at a *P*-value of 0.05 (2-tailed), and analyses were performed using STATA v9.1 (10).

RESULTS

Clinical Presentation

We reviewed 938 cases of NHL and HL. The patients were 60.1% male (95% CI: 56.9%–63.2%) and 39.9% female (95% CI: 36.8%–43.1%). The average age was 53.5 years (SD: ± 21.1) for men and 57.5 years (± 21.8) for women. Among all patients, 44% (40.1%–47.3%) had B-cell lymphoma, 46.4% (95% CI: 43%–49.5%) had HL, and 7.8% (95% CI: 6.1%–9.7%) had TCL. The most common lymphomas were DLBCL, FL, and nodular sclerosis classical Hodgkin lymphoma (NSCHL) with a respective prevalence of 17.2% (95% CI: 14.8%–19.7%), 14.1% (95% CI: 11.9%–16.5%), and 21.8% (95% CI: 19.1%–24.5%), respectively (Table 1). Among HL cases, 32% (95% CI: 37.3%–27.6%) were positive for EBV, and there was an increased association with mixed cellularity Hodgkin lymphoma and a decreased association with NLPHL (64.7% and 3.2%, respectively, *P* < 0.0001).

Table 2 summarizes NHL and HL sites of involvement. The most frequently involved sites were cervical lymph nodes (36.8% of all cases, 95% CI: 33.7%–40%), inguinal lymph nodes (16.4%, 95% CI: 14.1%–18.9%), axillary lymph nodes (11.9%, 95% CI: 9.9%–13.2%), and supraclavicular lymph nodes (11%, 95% CI: 9.1%–13.2%).

NHL and HL Prevalence by Nodal and Mediastinal Site of Involvement

For each nodal site and the extranodal mediastinal site, we examined the distribution of NHL and HL and reported the most frequent lymphomas in Table 3. Some nodal sites had a high prevalence of certain subtypes of lymphoma. For example, mediastinal lymph nodes were 15 times more likely to be classical Hodgkin lymphoma (CHL) compared to other sites

TABLE 1. Distribution of NHL and HL

Lymphomas	n (Total = 938)	%	95% CI
B-cell lymphoma			
DLBCL	161	17.2	14.8–19.7
T-cell rich DLBCL	11	1.2	0.6–2.1
Burkitt lymphoma	13	1.4	0.7–2.4
Follicular lymphoma	132	14.1	11.9–16.5
Mantle cell lymphoma	26	2.8	1.8–4.0
Nodal marginal zone B-cell lymphoma	14	1.5	0.9–2.5
B-cell prolymphocytic lymphoma	2	0.2	0–0.8
Anaplastic large B-cell lymphoma	1	0.1	0–0.6
CLL	40	4.3	3.1–5.8
LPL	11	1.2	0.6–2.1
Total	411	43.8	40.6–47.1
Hodgkin lymphoma			
CHL nos	42	4.5	3.2–6.0
NSCHL	204	21.8	19.1–24.5
NLPHL	84	9	7.2–11.0
MCHL	77	8.2	6.5–10.2
LRCHL	16	1.7	0.1–2.8
LDCHL	11	1.2	0.6–2.1
Total	434	46.3	43.0–49.5
T-cell lymphoma (TCL)			
TCL nos	37	3.9	2.8–5.4
Angioimmunoblastic TCL	14	1.5	0.9–2.5
T lymphoblastic lymphoma	8	0.9	0.4–1.7
Anaplastic large TCL	14	1.5	0.8–2.5
Total	73	7.8	6.1–9.7
Others			
	20	2.1	1.3–3.3

CHL = classic Hodgkin lymphoma, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, LDCHL = lymphocyte-depleted classical Hodgkin lymphoma, LPL = lymphoplasmocytic lymphoma, LRCHL = lymphocyte-rich classical Hodgkin lymphoma, MCHL = mixed cellularity Hodgkin lymphoma, n = number of cases, % = percentage of cases, 95% CI: 95% confidence interval, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, nos = not otherwise specified, NSCHL = nodular sclerosis classical Hodgkin lymphoma.

TABLE 2. Distribution of Nodal and Mediastinal Sites of Involvement in NHL and HL

Nodal Site of Involvement	n	%	95% CI
Cervical	345	36.8	33.7–40
Inguinal	154	16.4	14.1–18.9
Axillary	112	11.9	9.9–14.2
Supraclavicular	103	11	9.1–13.2
Retroperitoneal	67	7.1	5.6–9
Mediastinal	54	5.8	4.4–7.4
Intra-abdominal	53	5.7	4.3–7.3
Pelvic	15	1.6	0.9–2.6
Intrathoracic	11	1.7	0.6–2.1
Intraparotid	6	0.6	0.2–1.4
Retrosplinal	6	0.6	0.2–1.4
Mammary	3	0.3	0.1–1
Polyadenopathy	56	5.9	45.4–76.8
Mediastinum (total)	106	9.7	8.1–11.6
Mediastinum (nodal)	54	5.8	4.4–7.4
Mediastinum (extranodal)	52	5.8	4.2–7.2

% = percentage of cases, 95% CI = 95% confidence interval, n = number of cases.

(OR: 15, 95% CI: 6.3–37.6, multiple test corrected *P*-value [*c-P*] = 0.0001). Similarly, supraclavicular nodes were more frequently involved in CHL (OR = 2.1, 95% CI: 1.4–3.2, *c-P* = 0.004) and TCL most often displayed polyadenopathy (OR = 4.6, 95% CI: 2.1–9.6, *c-P* = 0.0001).

On the other hand, CHL was uncommon in inguinal nodes (OR = 0.6, 95% CI: 0.4–0.8, *c-P* = 0.034) (Table 3). These results are consistent with known associations, especially between CHL and cervical nodes and between supraclavicular nodes and nodal or extranodal mediastinal sites. However, we also found an unexpected but interesting and significant association of intraparotid nodes with NLPHL (OR = 21.3, 95% CI: 3–237, *c-P* = 0.011) and inguinal nodes with FL (OR = 1.9, 95% CI: 1.2–2.9, *c-P* = 0.0345).

We also studied the distribution of HL subtypes among the 392 HL cases in which it was documented. We observed that mediastinal sites (nodal or extranodal) and supraclavicular nodes were more likely to be associated with NSCHL (OR = 8.9, 95% CI: 4–20.2, *c-P* = 0.0001 and OR = 3.2, 95% CI: 1.6–6.2, *c-P* = 0.002, respectively). Inguinal sites were associated with NLPHL (OR = 2, 95% CI: 1.1–3.7); however, this result was not significant after adjustments for multiple testing. NSCHL was found less frequently in inguinal nodes (OR = 0.4, 95% CI: 0.2–0.7, *c-P* = 0.008), whereas NLPHL was less frequent in mediastinal and supraclavicular sites

TABLE 3. Distribution of the Most Frequent NHL and HL by Nodal and Extranodal Sites of Involvement

	n	%	OR	OR 95% CI	P	c-P		n	%	OR	OR 95% CI	P	c-P
Polyadenopathy (n = 56)							Mediastinum (nodal and extranodal) (107)						
CHL	4	25	0.5	0.3–1.0	0.0496*	ns	CHL	77	72.6	4.7	3.0–7.4	<0.00001*	0.0001
TCL	12	21.4	4.6	2.1–9.6	<0.00001**	0.0001	DLBCL	18	17.0	0.9	0.5–1.5	ns*	ns
FL	9	16.1	1.2	0.6–2.5	ns*	ns	TCL	5	4.7	0.7	0.3–1.7	ns*	ns
DLBCL	9	16.1	0.8	0.4–1.8	ns	ns	Nodal mediastinal (54)						
Intrathoracic and mammary (14)							CHL	48	88.9	15.4	6.3–37.6	<0.00001*	0.0001
CHL	4	28.6	1	0.2–3.8	ns**	ns	DLBCL	4	7.4	0.3	0.1–1.0	0.0326*	ns
CLL	3	21.4	5.2	0.5–26.3	ns**	ns	Extranodal mediastinal (55)						
Intraabdominal (53)							CHL	29	52.7	2	1.1–3.4	0.0149*	ns
CHL	16	30.2	0.7	0.4–1.3	ns*	ns	DLBCL	14	25.5	1.6	0.8–3	ns*	ns
DLBCL	11	20.8	1.2	0.6–2.3	ns*	ns	TCL	5	9.1	1.5	0.6–3.9	ns*	ns
FL	10	18.9	1.5	0.7–3.0	ns*	ns	Pelvic (15)						
Retrosplinal (6)							CHL	4	26.7	0.6	0.2–1.9	ns*	ns
CHL	5	83.3	8.5	0.9–403	ns**	ns	FL	4	26.7	2.3	0.5–7.8	ns**	ns
FL	1	16.7	1.2	0–11.1	ns**	ns	Cervical (345)						
Axillary (112)							CHL	144	41.7	1.3	1–1.8	0.0326*	ns
CHL	31	27.7	0.6	0.4–0.9	0.0247*	ns	DLBCL	63	18.3	1	0.7–1.4	ns*	ns
DLBCL	20	17.9	1	0.6–1.6	ns*	ns	NLPHL	40	11.6	1.6	1–2.6	0.0309*	ns
FL	19	17	1.3	0.8–2.2	ns*	ns	FL	33	9.6	1.4	0.5–3.3	ns*	ns
NLPHL	13	11.6	1.4	0.7–2.6	ns*	ns	Supraclavicular (103)						
Inguinal (154)							CHL	55	53.4	2.1	1.4–3.2	0.0003*	0.0044
CHL	41	26.6	0.6	0.4–0.8	0.0027*	0.0345	DLBCL	17	16.5	0.9	0.5–1.5	ns*	ns
FL	33	21.4	1.9	1.2–2.9	0.0041*	0.0345	FL	11	10.7	0.7	0.4–1.4	ns*	ns
DLBCL	21	13.6	0.7	0.4–1.1	ns*	ns	CLL	7	6.8	1.8	0.6–4.2	0.005**	0.0367
NLPHL	18	11.7	1.4	0.8–2.5	ns*	ns	NLPHL	4	3.9	0.4	0.1–1.1	ns*	ns
TCL	14	9.1	1.6	0.8–2.9	ns*	ns	Intraparotid (6)						
Retroperitoneal (67)							NLPHL	4	66.7	21.3	3.0–237.0	0.0008**	0.0117
CHL	24	35.8	0.9	0.6–1.6	ns*	ns	FL	1	16.7	1.2	0.03–11.1	ns**	ns
DLBCL	18	26.9	1.7	1–3.0	ns*	ns	DLBCL	1	16.7	0.9	0–8.0	ns**	ns
FL	14	20.9	1.7	0.9–3.1	ns*	ns							

95% CI = 95% confidence interval, CHL = classic Hodgkin lymphoma, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, n = number of cases (a single case of lymphoma could involve several sites), NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, TCL = T-cell lymphoma. c-P: corrected P-value using Benjamini-Hochberg false discovery rate under general dependence.

OR: odds ratio between the observed prevalence of NHL and LH in the specific nodal or mediastinal site to its prevalence in all other sites.

P: P-value calculated using a chi-squared or Fisher exact test comparing the observed prevalence of NHL and LH in the specific nodal or mediastinal sites to its prevalence in all other sites. *Chi-squared test, **Fisher exact test.

(OR = 0, 95% CI: 0–0.17, c-P = 0.0001; OR = 0.2, 95% CI: 0.1–0.7, c-P = 0.03, respectively) (Table 4). Additionally, we did not find any association between EBV infection and the site of involvement (data not shown).

Some lymphomas occurred at different frequencies in males and females, and some were linked to age. Younger patients of both sexes with cervical or supraclavicular node involvement were most likely to have HL, whereas in older patients, the most common diagnosis was DLBCL. Furthermore, for male patients, especially younger ones, NLPHL was also common at these sites. Similarly, FL and NLPHL with inguinal node involvement were common diagnoses in younger patients irrespective of sex (Tables 5 and 6).

Because age and sex might be confounding factors, we adjusted ORs for age and sex. After adjustment, the association between the following sites and diagnoses remained significant (Table 7): polyadenopathy and TCL (aOR: 3.8, [1.8–8.2]);

inguinal nodes and FL (aOR: 1.7 [1.1–2.7]); inguinal nodes and CHL (aOR: 0.6, 95% CI: 0.4–0.96); mediastinal site and CHL (aOR: 4, 95% CI: 2.5–6.4); supraclavicular nodes and CHL (aOR: 1.9, 95% CI: 1.2–3); intraparotid nodes and NLPHL (aOR: 19.1, 95% CI: 3.1–117.2). However, the aOR for the association between chronic lymphocytic leukemia (chronic lymphoid leukemia) and supraclavicular nodes was no more significant. With respect to HL, the aOR for the association between mediastinal site and NSCHL was 7.5 [3.4–16.3]; the aOR for supraclavicular node and NSCHL was 3.1 (95% CI: 1.6–6); and the aOR for supraclavicular node and NLPHL was 0.3 (95% CI: 0.09–0.7).

DISCUSSION

Our study shows that the distribution of various NHLs and subtypes of HL strongly depends on the specific nodal site of

TABLE 4. Distribution of Different Subtypes of HL by Site of Involvement

	n	%	OR	OR 95% CI	P	c-P		n	%	OR	OR 95% CI	P	c-P
Polyadenopathy (n = 14)							Intrapancreatic (4)						
NLPHL	3	21.4	1	0.8–3.9	ns**	ns	NLPHL	4	100	-***	3.94***	0.002**	0.0228
NSCHL	6	42.9	0.7	0.2–2.0	ns*	ns	NSCHL	0	0	0	0–0.87***	0.05**	ns
MCHL	5	35.7	2.4	0.6–8.1	ns**	ns	MCHL	0	0	0	0–3.9***	ns**	ns
LRCHL	0	0	0	0–6.4***	ns**	ns	LRCHL	0	0	0	0–23.7***	ns**	ns
LDCHL	0	0	0	0–9.6***	ns**	ns	LDCHL	0	0	0	0–35.8***	ns**	ns
Intrathoracic and mammary (4)							Mediastinal (42)						
NLPHL	0	0	0	0–3.5***	ns**	ns	NLPHL	0	0	0	0–0.3***	0.00001**	0.0001
NSCHL	3	75	2.8	0.2–147.3	ns**	ns	NSCHL	37	88.1	8.1	3–21.8	0.00001*	0.0001
MCHL	1	25	1.2	0–17.3	ns**	ns	MCHL	5	11.9	0.5	0.2–1.4	ns*	ns
LRCHL	0	0	0	0–23.7***	ns**	ns	LRCHL	0	0	0	0–1.9***	ns**	ns
LDCHL	0	0	0	0–35.8***	ns**	ns	LDCHL	0	0	0	0–2.9***	ns**	ns
Intraabdominal (18)							Retroperitoneal (18)						
NLPHL	2	11.1	0.4	0–2	ns**	ns	NLPHL	2	11.1	0.4	0–2	ns**	ns
NSCHL	9	50	0.9	0.4–2.4	ns*	ns	NSCHL	8	44.4	0.7	0.3–1.9	ns*	ns
MCHL	1	5.6	0.2	0–1.5	ns**	ns	MCHL	6	33.3	2.1	0.6–6.4	ns**	ns
LRCHL	2	11.1	3.2	0.3–15.9	ns**	ns	LRCHL	0	0	0	0–4.9***	ns**	ns
LDCHL	4	22.2	15	2.8–66.3	ns**	ns	LDCHL	2	11.1	5.1	0.5–27.4	ns**	ns
Retrosplenic (4)							Pelvic (4)						
NLPHL	0	0	0	0–3.5***	ns**	ns	NLPHL	1	25	1.2	0–15.5***	ns**	ns
NSCHL	3	75	2.8	0.2–147.3	ns**	ns	NSCHL	2	50	0.9	0.1–12.8	ns**	ns
MCHL	1	25	1.4	0–17.3	ns**	ns	MCHL	1	25	1.4	0.3–17.3	ns**	ns
LRCHL	0	0	0	0–23.7***	ns**	ns	LRCHL	0	0	0	0–23.7***	ns**	ns
LDCHL	0	0	0	0–35.8***	ns**	ns	LDCHL	0	0	0	0–35.8***	ns**	ns
Axillary (39)							Cervical (169)						
NLPHL	13	33.3	2	1–4.1	ns*	ns	NLPHL	40	23.7	1.3	0.8–2	ns*	ns
NSCHL	14	35.9	0.5	20.2–1	0.0337*	ns	NSCHL	86	50.9	0.9	0.6–1.4	ns*	ns
MCHL	8	20.51	1.1	0.5–2.4	ns*	ns	MCHL	36	21.3	1.2	0.7–2	ns*	ns
LRCHL	3	7.7	2.2	0.4–8.4	ns**	ns	LRCHL	4	2.4	0.4	0.1–1.4	ns*	ns
LDCHL	1	2.6	0.9	0–6.7	ns**	ns	LDCHL	3	1.8	0.5	0.1–2.1	ns**	ns
Inguinal (55)							Supraclavicular (56)						
NLPHL	18	32.7	2	1.1–3.7	0.0278*	ns	NLPHL	4	7.1	0.2	0.1–0.7	0.0049*	0.0279
NSCHL	17	30.9	0.4	0.2–0.7	0.0007*	0.008	NSCHL	42	75	3.2	1.6–6.2	0.0002*	0.0023
MCHL	13	23.6	1.3	0.7–2.6	ns*	ns	MCHL	7	12.5	0.5	0.2–1.3	ns*	ns
LRCHL	4	7.3	2.1	0.5–7.3	ns**	ns	LRCHL	3	5.4	1.4	0.2–5.4	ns**	ns
LDCHL	3	5.5	2.4	0.4–10.3	ns**	ns	LDCHL	0	0	0	0–2.1***	ns**	ns
Extranodal mediastinal (26)							Total (n = 392)						
NLPHL	0	0	0	0–0.5***	0.0023**	0.0011	95% CI						
NSCHL	23	88.5	7.8	2.3–27.3	0.0001*	0.0131	NLPHL	84	21.4	17.5–25.8			
MCHL	3	11.5	0.5	0.1–1.8	ns*	ns	NSCHL	204	52	47–57.1			
LRCHL	0	0	0	0–3.3***	ns**	ns	MCHL	77	19.6	15.8–23.9			
LDCHL	0	0	0	0–4.9***	ns**	ns	LRCHL	16	4.1	2.4–6.5			
							LDCHL	11	2.87	1.4–5			
Mediastinal (nodal and extra) (66)													
NLPHL	0	0	0	0–0.17***	0.00001*	0.0001							
NSCHL	58	87.9	8.9	4–20.2	0.00001*	0.0001							
MCHL	8	12.1	0.5	0.2–1.1	ns*	ns							
LRCHL	0	0	0	0–1.1***	ns**	ns							
LDCHL	0	0	0	0–1.7***	ns**	ns							

95% CI = 95% confidence interval, CHL = classical Hodgkin lymphoma, LDCHL = lymphocyte-depleted classical Hodgkin lymphoma, LRCHL = lymphocyte-rich classical Hodgkin lymphoma, MCHL = mixed cellularity Hodgkin lymphoma, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, NSCHL = nodular sclerosis classical Hodgkin lymphoma. c-P: corrected P-value, using Benjamini-Hochberg false discovery rate.

***: 95% CI calculated using Cornfield test (when the number of cases = 0).

OR: odds ratio between the observed prevalence of the different subtypes of LH in a specific nodal or mediastinal site to its prevalence in all other sites.

p: p-value calculated using a chi-square or Fisher exact test comparing the observed prevalence of the different subtypes of LH in the specific nodal or mediastinal site to its prevalence in all other sites. *Chi-square, **Fisher exact test.

TABLE 5. Distribution of Different Subtypes of HL by Site of Involvement

Female <60	n	%	Female ≥60	N	%
Cervical (n = 62)			Cervical (52)		
CHL	44	71	DLBCL	15	28.9
DLBCL	4	6.5	CHL	9	17.3
FL	2	5	FL	8	15.4
Supraclavicular (26)			Supraclavicular (19)		
CHL	20	76.9	DLBCL	6	31.6
FL	3	11.5	CHL	5	26.3
DLBCL	2	7.7	FL	6	21.4
Axillary (8)			Axillary (34)		
CHL	4	50	FL	8	23.5
NLPHL	2	25	DLBCL	7	20.6
FL	1	12.5	CHL	4	11.8
Mediastinal (38)			Mediastinal (12)		
CHL	30	79	CHL	6	50
DLBCL	4	10.5	DLBCL	3	25
TCL	1	2.6	TCL	1	8.3
Inguinal (21)			Inguinal (29)		
FL	6	28.6	FL	11	37.9
NLPHL	5	23.8	CHL	5	17.2
CHL	4	19.1	TCL	2	6.9
Deep nodes below the diaphragm (26)			Deep nodes below the diaphragm (35)		
CHL	12	46.1	CHL	9	25.7
FL	7	26.9	FL	7	20
DLBCL	3	11.5	DLBCL	9	25.7

CHL = classic Hodgkin lymphoma, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, TCL = T-cell lymphoma. Total number of cases per sites and percentage were calculated including missing values (not shown).

involvement. We reviewed 938 consecutive cases of NHL and HL and reported the nodal sites of involvement for each case. Previous studies have looked at sites of involvement in lymphoma,^{6,7,11-13} but may be limited by focusing on a specific lymphoma subtype or on a specific outcome. To our knowledge, none has systematically correlated these sites with common NHL and HL subtypes. Our descriptive study characterizes the distribution of lymphomas at each site and the preferential localization of each lymphoma. A limitation of this study is that not all lymph nodes may have been tested at diagnosis and no data on the disease stage was available. Consequently, we could not determine the site of origin of the tumor with certainty. However, we believe that the lymph nodes used to make the diagnosis are generally the largest found and are thus likely to be located in one of the primary sites of the disease. To assess the potential bias from excluding diagnoses with an unspecified location, we compared our sample with the excluded sample for age, sex, and lymphoma subtypes and did not find any significant differences (data not shown). Additionally, due to the retrospective design of our study, we were unable to adjust our results for other potentially confounding factors (other than age and sex), such as history of viral infection, that could influence the site of involvement. Despite these limitations, our results provide interesting clues for further investigation.

TABLE 6. Adult Male (15 to 60-years old) Distribution of the Most Frequent NHL and HL by Site of Involvement and Age

Male <60	N	%	Male ≥60	n	%
Cervical (115)			Cervical (71)		
CHL	58	50.4	DLBCL	20	28.2
NLPHL	22	19.1	CHL	18	25.6
DLBCL	16	13.9	CLL	9	12.7
Supraclavicular (32)			Supraclavicular (15)		
CHL	20	62.5	DLBCL	5	33.3
DLBCL	3	9.4	CHL	4	26.7
FL	2	6.2	CLL	3	20
Axillary (28)			Axillary (34)		
CHL	13	46.4	CHL	8	23.5
NLPHL	7	25	FL	8	23.8
DLBCL	2	7.1	DLBCL	8	23.5
Mediastinal (38)			Mediastinal (11)		
CHL	27	71.1	CHL	6	54.6
DLBCL	7	18.4	DLBCL	3	27.3
TCL	3	7.9			
Inguinal (35)			Inguinal (60)		
CHL	10	28.6	CHL	20	33.3
NLPHL	8	22.9	DLBCL	15	25
FL	8	22.9	FL	5	8.3
Deep nodes below the diaphragm (30)			Deep nodes below the diaphragm (37)		
CHL	13	43.3	CHL	12	32.4
DLBCL	6	20	DLBCL	9	24.3
FL	4	13.3	FL	8	21.6

CHL = classic Hodgkin lymphoma, CLL = chronic lymphocytic leukemia, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, TCL = T-cell lymphoma, mediastinal: nodal and extranodal sites.

Total number of cases per sites and percentage were calculated including missing values (not shown).

As lymphomas are heterogeneous, data on the preferential localization of each type will aid in early clinical diagnosis. For example, a lymphoma primarily associated with inguinal lymph nodes in a male under 60 is more frequently CHL or NLPHL compared with older males where it is more likely CHL. As the prognosis of these 2 subtypes of HL is quite different, rapid differential diagnosis is essential. Among females that are 60 years or older, the most frequent diagnosis associated with an inguinal primary site is FL, comprising about 37% of the cases, compared to 21% in the general population. Interestingly, FL is more frequent in inguinal sites among females (regardless of age) than among males. Likewise, an intraparotid lymphoma was diagnosed as NLPHL in 66% of cases, while the overall prevalence of this subtype was only 9%. These findings suggest that some lymphomas may have preferential primary sites of involvement.

As the causes of most lymphoid neoplasms remain unknown, analyses of these preferential nodal sites may provide clues to their etiology. Among potential environmental etiologies, the well-studied is infection.¹⁴⁻¹⁶ Infection may increase proliferation and decrease apoptosis of lymphoid cells and thus contribute to lymphocyte transformation. The role of EBV in HL pathogenesis is now well established.¹⁷⁻²² Furthermore,

TABLE 7. Nodal Sites of Involvement by Lymphoma Type

Site of Involvement	FL		DLBCL		TCL		NLPHL		NSCHL		MCHL		LRCHL		LDCHL	
	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)	%	(n)
Parotid	0.8	(1)	0.6	(1)	0	(0)	4.8	(4)	0	(0)	0	(0)	0	(0)	0	(0)
Intrathoracic and mammary	1.6	(2)	1.2	(2)	0	(0)	0	(0)	1.5	(3)	1.3	(1)	0	(0)	0	(0)
Mediastinal	0	(0)	10.4	(18)	8.2	(5)	0	(0)	29.4	(60)	10.4	(8)	0	(0)	0	(0)
Deep nodes below the diaphragm	20.5	(27)	17.44	(30)	4.9	(3)	5.6	(5)	10.8	(22)	11.7	(9)	12.5	(2)	45.5	(5)
Axillary	14.4	(19)	11.6	(20)	16.4	(10)	15.5	(13)	6.9	(14)	10.4	(8)	18.8	(3)	9.1	(1)
Inguinal	25	(33)	12.21	(21)	23	(14)	21.4	(18)	8.3	(17)	16.9	(13)	25	(4)	27.3	(3)
Cervical	25	(33)	36.6	(63)	26.2	(16)	47.6	(40)	42.2	(86)	46.8	(36)	25	(4)	27.3	(3)
Supraclavicular	8.3	(11)	9.9	(17)	8.2	(5)	4.8	(4)	20.6	(42)	9.1	(7)	18.8	(3)	0	(0)

DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, LDCHL = lymphocyte-depleted classical Hodgkin lymphoma, LRCHL = lymphocyte-rich classical Hodgkin lymphoma, MCHL = mixed cellularity Hodgkin lymphoma, mediastinal = nodal and extranodal sites, NLPHL = nodular lymphocyte predominant Hodgkin lymphoma, NSCHL = nodular sclerosis classical Hodgkin lymphoma, TCL = T-cell lymphoma.

O’Grady et al²³ showed that the prevalence of EBV in HL is related to the site of origin of the tumor and was higher in nodes draining tonsillar and oropharyngeal lymphoepithelial tissue. These findings are not surprising because the oropharyngeal epithelium is the main site of EBV proliferation after infection, although latently infected B-cells in circulation also carry the virus and account for EBV-positive tumors in nonneck sites. Another study²⁴ indicated that EBV-associated TCLs were highly site restricted, nasal TCLs were EBV-associated, whereas pulmonary and gastrointestinal TCLs were less frequently associated with EBV. Hence, TCLs arising from different sites but with similar morphology may show differences in lymphomagenesis.

Extending this concept, the predilection of lymphomas for specific sites of involvement might be consistent with certain tissue-specific infections. Two mechanisms are often proposed to explain how infection can induce lymphoma. First, some viral agents, such as EBV and human herpes virus 8 (HHV8),^{25,26} are able to directly infect and transform lymphocytes due to the expression of oncogenes. Second, other infections may induce chronic immune stimulation, including the persistent activation of lymphocytes, which may increase the risk of lymphoma. This model of antigen-driven lymphoproliferation has been described particularly in infection-associated lymphomas derived from marginal zone B cells²⁷ the best example being gastric mucosa-associated lymphatic tissue lymphoma associated with helicobacter pylori. The presence of preferential primary nodal sites of involvement is consistent with a chronic site-specific infection, a persisting antigen or an unknown lymphotropic-transforming pathogen that might be at play in the process of lymphomagenesis.

In conclusion, our study shows that some lymph node sites have a disproportionate prevalence of specific subtypes of lymphoma. Identifying these sites may aid to diagnose and

better elucidate the pathogenesis of these tumors. In particular, these nodal areas may represent specific entry sites for putative triggering antigens.

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