

# Extranodal Location of Lymphoma: Presentation and Evolutionary in Senegalese Patients

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## Abstract

**Introduction:** The frequency of extranodal involvement in lymphoma is not rare, but variously described by authors in Africa. The objective of our work is to describe the profile of patients followed for lymphoma with extranodal locations. **Methods:** We conducted a descriptive, retrospective and analytic study at the clinical hematology department of Dalal Jamm Hospital, from September 2016 to June 2022. We included patients with a diagnosis of lymphoma immunohistochemistry, with extranodal involvement. The epidemiological, diagnostic, prognostic and survival aspects were studied. **Results:** Fifty-two (52) patients with extranodal localizations of their lymphoma were included. The mean age was  $44.2 \pm 17.6$  years and the sex ratio was 1.2. The average time to diagnostic was  $9.4 \pm 3.6$  months. We found a performance status  $\geq 2$  in 65.4% and at least one B symptom in 71.2% of cases. The extranodal manifestations were digestive (19%), cutaneous (17.5%), pleuropulmonary (17.5%), bone marrow (4.8%), thyroid (1.6%), parotid gland (1.6%) and breast (1.6%). Patients presented with Hodgkin's lymphoma (HL) in 19.2% of cases and non-Hodgkin's lymphoma (NHL) in 80.8% of cases. At the end of the extension checkup reviews, 61.5% were at an advanced stage and prognostic indices were unfavorable in 32% of patients. Conventional chemotherapy was conducted in 63.5% of patients of which 24 had NHL and 9 had HL. Immuno-chemotherapy was used in 26.9% of patients (13 cases of NHL, 1 case of HL). During the follow-up, we noted only 29.7% of complete remission. The median overall survival was 25.1 months [23.5 - 34.1 months] in HL group and 20.5 months [18.7 - 72.2 months] in NHL patients ( $p = 0.14$ ). **Conclusion:** Our study shows that extranodal involvements of lymphomas are various, encountered more during NHL. In our practice, diagnosis is generally made at an advanced stage, with poor response to treatment.

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## Keywords

Lymphoma, Extranodal Involvement, Advanced Stage, Senegal

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## 1. Introduction

Lymphomas are malignant hemopathies characterized by the clonal proliferation of lymphoid cells. A distinction is mainly made between Hodgkin's lymphoma and non-Hodgkin's lymphoma (B, T, NK) [1]. Extranodal lymphoma is defined as all the manifestations related to the infiltration of non-nodal lymphoid tissue by lymphoma cells [1]. Its frequency is variable, between 24% and 48%, according to the data available in the literature [2]. In sub-Saharan Africa, the frequency was globally estimated at 18.6% [3], reaching 80% in AIDS patients [4]. Extranodal lymphoma can affect any organ. Digestive lymphomas are the most frequent extranodal sites, representing 30% - 40% of NHLs [5]. The presentation of extranodal lymphomas is polymorphic with various sites: cutaneous, central nervous system, ENT, pleuropulmonary, etc [5]. Diffuse large B cell lymphoma (DLBCL) account for about one-third of extranodal involvement [1] [6]. Moreover, during certain NHLs, extranodal localizations of the disease are specific. MALT (Mucosa Associated Lymphoma Tissue) lymphomas have been described with digestive, thyroid, cutaneous and ocular involvement [1]. Treatment options are represented by chemotherapy sometimes associated with immunotherapy, surgery and radiotherapy. A poor outcome has been reported with extranodal localizations of lymphomas, with less overall survival ( $p = 0.003$ ) despite the same progression free survival ( $p = 0.8$ ) [7]. Data on the extra-nodal manifestations of lymphoma are patchy and have not been specifically studied in sub-saharan patients particularly in Senegal. Thus, we conducted this study with the objective of assessing the management and outcomes of patients with extra-nodal lymphoma.

## 2. Methods

### 2.1. Type and Setting of the Study

We conducted a descriptive and retrospective study from September 2016 to June 2022 at the Clinical Hematology Service of Dalal Jamm Hospital (Senegal) which is a reference center in onco-hematology, in a level 3 university hospital. During this period, 113 cases of lymphomas were treated in hospitalization and outpatient ward.

### 2.2. Patients

We collected data from the files of all the patients hospitalized and followed ambulatory for lymphoma with extranodal localization. Confidentiality and anonymity have been assured during the process. The diagnosis of lymphoma was clinically and/or radiologically suspected (CT Scan, Magnetic Resonance Imaging), then retained on pathological examination which included immunos-

taining (immunohistochemistry, immunophenotyping) and/or fluorescence in situ hybridization from organ biopsies. Samples were sent by private laboratories in Senegal to dedicated pathology laboratories in France. The diagnosis of HL or NHL was made on the basis of the 2016 WHO (World Health Organization) criteria [8]. Primary involvement was described as occurring in a non-nodal organ or tissue with or without involvement of adjacent or draining lymph nodes. The tumor mass was assessed using the Ann Arbor classification [9], and Musshoff for MALT with digestive location [10]. The prognostic factors for NHL were aa-IPI (Age Adjusted International Prognostic Index). For HL we used the EORTC (European Organization for Research and Treatment of Cancer) index in the case of localized forms and IPS (International Prognostic Score) in the case of advanced forms [11]. Depending on their financial situation, NHL patients received either conventional chemotherapy: CHOP (Cyclophosphamide, doxorubicin, Adriablastin, Prednisone); COP (Cyclophosphamide, vincristine, Prednisone); ACVP (Bleomycin, Cyclophosphamide, Adriablastin, vincristine, Prednisone) or immunochemotherapy (Rituximab plus conventional chemotherapy). All HL patients were treated with ABVD (Adriablastin, bleomycin, Vinblastine, Decitabine). According to their response to treatment, patients were classified as having complete response (CR), uncertain complete response (UCR), partial response (PR), stable disease (SD) and progressive disease (PD) based on Cheson's criteria [12]. The absence of remission included SD and PD [12]. Patients with incomplete and non-usable data were excluded from this study.

Analysis: we collected data related to socio-epidemiological status (age, gender, comorbidities), diagnostic (sites of lymphomas, Cooperative Oncology Group Performance Status: ECOG PS), pathological subtypes of lymphoma (B-cell NHL, T-cell NHL, HL), prognosis (Ann Arbor stages, Musshoff stages, prognostic index), therapeutic (chemotherapy, immunochemotherapy) and outcome (response to treatment, survival). We expressed data as frequency, means  $\pm$  standard deviations, median and extremes. The outcome was assessed by median survival with Kaplan Meier curve and log Rank test (considered statistically significant with  $p$ -value  $< 0.05$ ); patients who were lost to follow-up were not included in the analysis. All analyses were performed using SPSS (Statistical Package for the Social Sciences) version 21.0 software.

### 3. Results

Concerning socio-epidemiologic data (Table 1), a total of 52 patients were included (28 men and 24 women), with a sex-ratio of 1.2. The mean age (Table 1), was  $44.25 \pm 17.6$  years (extremes: 18 - 80 years) for all patients, and  $32 \pm 11$  years (extremes: 18 - 65 years) for HL patients. Toxic exposure was seen with chemical fertilizers (13.4%), long-term phytotherapy (5.8%) and hydrocarbons (3.8%). Comorbidities were diabetes (11.5%), hypertension (5.7%) and HIV infection (3.8%).

Looking at the diagnostic aspects, the mean time from the first symptoms to the confirmation of the diagnosis was  $9.4 \pm 4.8$  months. According by ECOG PS

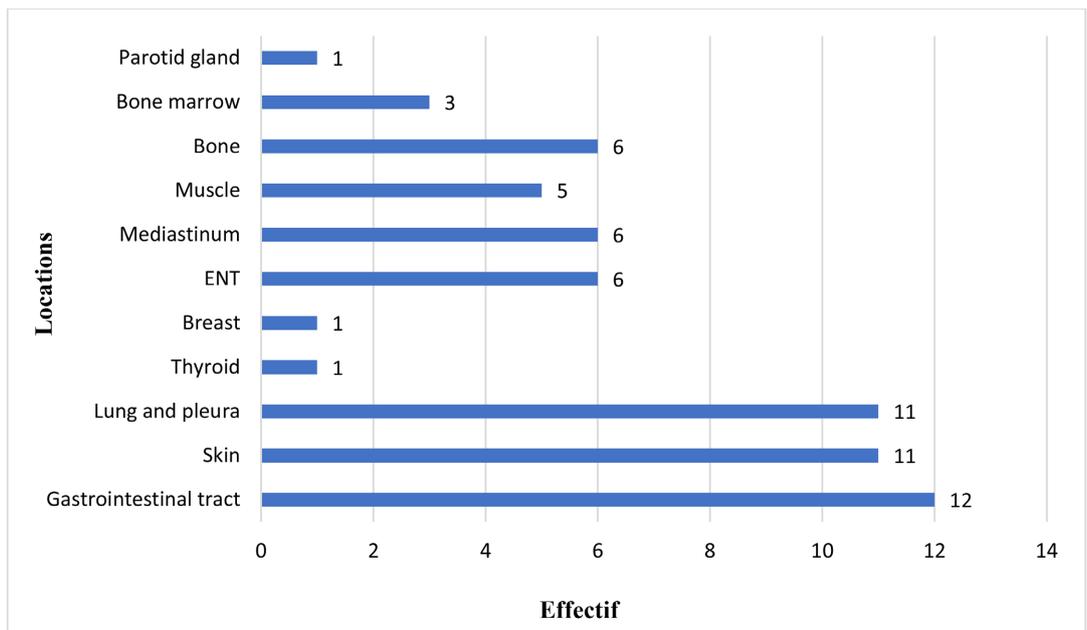
score, 65.4% of patients had a score of more than 2. The signs of lymphoma progression, also called B symptoms, were present in 71.2% of cases. We observed a total of 63 extranodal sites in our patients of whom 82.3% were isolated and 17.7 % were multiple.

The extranodal manifestations (**Figure 1**) were digestive (19%), cutaneous

**Table 1.** Socio-epidemiologic and general characteristics of extra nodal lymphomas in Senegalese patients.

Parameters		NHL (N = 28)	HL (N = 24)	Total patients (N = 52)
mean ± Standard Deviation (extremes)				
Age: (years)		51 ± 18 (20 - 80)	32 ans ± 11 (18 - 65)	44.25 ± 17.6 (18 - 80)
n/N (%)				
Gender:	M	15 (53,6)	13 (54,2)	28 (53,8)
	W	13 (46,4)	11 (45,8)	24 (46,2)
Comorbidities:	Diabetes	6 (21,4)	0 (0)	6 (11,5)
	Hypertension	2 (7,1)	1 (4,2)	3 (5,7)
	HIV	1 (3,6)	1 (4,1)	2 (3,8)
ECOG PS score:	1 - 2	10 (35,7)	8 (33,3)	18 (34,6)
	3 - 4	18 (64,3)	16 (66,7)	34 (65,4)

NHL: Non Hodgkin Lymphoma, HL: Hodgkin Lymphoma; M: man, W: Woman; HIV: Human Immunodeficiency Virus; ECOG PS: Cooperative Oncology Group Performance Status.



ENT: Ear Nose Throat

**Figure 1.** Number and distribution of visceral involvement of extranodal lymphomas in Senegalese patients.

(17.5%), pleuropulmonary (17.5%). Some patients presented with bone marrow (4.8%), thyroid (1.6%), parotid gland (1.6%) and breast (1.6%) involvements. The clinical presentation was site dependent. Other findings related to the lymphoma were tumoral lymphadenopathies, splenomegaly and hepatomegaly respectively in 64.4%, 11.5% and 7.7% of cases.

For blood count abnormalities, we found anemia in 75.6% of cases, with an average hemoglobin level of  $11 \pm 2$  g/dl. It was present in all digestive location and all bone marrow involvements. The average of white blood cell count was  $20 \pm 25$  G/l and the average platelet count was  $325.4 \pm 152.9$  G/l.

According to histologic subtypes (**Table 2**), NHL was predominant with 80.8% of cases, involving B cells (53.9%) and T cells (26.9%). HL was found in 19.2% of cases (10 cases), all presenting as the classic form on histology. Extranodal location was primary in 73.1%, and secondary as part of a disseminated lymphoma in 26.9%.

Tumor assessment according to Ann Arbor classification, noted that patients were at stage IV (60.9%), stage III (12 %), stage II (10.1%) and stage I (17%). For gastrointestinal tract MALT lymphomas (n = 4), patients were all at advanced stages: IIE (25%) and IV (75%). The other sites of MALT lymphomas were the thyroid gland (1 case) and parotid gland (1 case). The entities being multiple, and different prognostic scores are summarized in **Table 3**. Advanced stages are observed in DLBCL (50%), FL (50%), T-cell NHL (42.9%) and HL (60%) (**Table 3**).

**Table 2.** Anatomoclinic and phenotypic entities of extranodal lymphomas in Senegalese patients.

Type of lymphoma	Entities	n	(%)
B-cell NHL (N = 28)	DLBCL	15	(53.6)
	MALT	6	(21.4)
	Follicular	5	(17.9)
	Unspecified	2	(7.1)
T-cell NHL (N = 14)	Anaplastic.	3	(21.5)
	Lymphoblastic	2	(14.3)
	Sezary Syndrom	2	(14.3)
	CD30+ NOS	1	(7.1)
	Peripheral	1	(7.1)
	Unspecified	5	(35.7)
HL (N = 10)	Scelonodular	8	(80)
	Lymphocyte-rich	2	(20)

N: Total number; n: effectif concerned, DLBCL: Diffuse Large B Cell lymphoma; MALT: Mucosa Associated lymphoid Tissue; B-cell NHL: B-cell non Hodgkin Lymphoma; T-cell NHL: T-cell non Hodgkin Lymphoma; HL: Hodgkin lymphoma.

**Table 3.** Distribution of patients according to prognostic score of extranodal lymphomas in Senegalese.

Type of lymphoma	Score	Risk Group	n	(%)
DLBCL (N = 6)	aaIPI	Low	1	(16.7)
		Intermediary	2	(33.3)
		High	3	(50)
FL (N = 4)	FLIPI	Low	1	(25)
		Intermediary	1	(25)
		High	2	(50)
Mantle NHL (N = 3)	MIPI	Intermediary	2	(66.7)
		Low Intermediary	1	(33.3)
T-cell NHL (N = 7)	IPI T	High Intermediary	4	(57.1)
		High	3	(42.9)
HL (N = 10)	EORTC	Unfavorable	1	(10)
	IPS	Unfavorable	6	(60)
	Unapplied		3	(30)

N: Number evaluated, n: effectif concerned, aa-IPI: Age Adjusted International Prognostic Index; FLIPI: Follicular Lymphoma International Pronostic Index; MIPI: Mantle Cell lymphoma International Prognostic Index; IPI T: International Prognostic Index for T-Cell NHL, EORTC: (European Organization for Research and Treatment of Cancer), IPS: International Pronostic Score. DLBCL: Diffuse Large B Cell lymphoma; Mantle NHL: Mantle Cell lymphoma; T-cell NHL: T-cell non Hodgkin Lymphoma; HL: Hodgkin lymphoma.

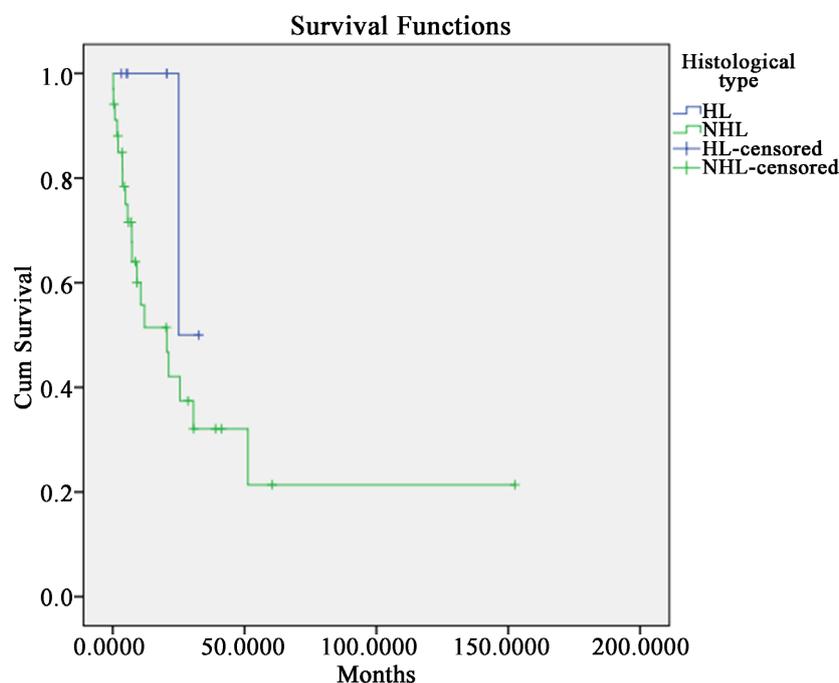
Regarding the treatment, conventional chemotherapy was used in 24 cases of NHL and 9 cases of HL. Immunotherapy with Rituximab was given in 13 cases of NHL and 1 case of HL. Adjuvant treatment involved surgical resection in 8 cases of digestive localizations, radiotherapy in 2 cases of spinal localizations and decompressive laminectomy in 1 case.

During the follow-up, we noted 29.7% complete remission (n = 11), 67.6% partial remission (n = 25) and 30.7% with no remission. The mortality rate was 38.5% in our study.

The median overall survival in our study was 20.5 months [18.7 - 72.2 months]. According to the Kaplan Meier curve, the probability of survival at the end of the study was, 48% for HL patients and 20% for NHL patients. In analytical study, the median survival was 25.1 months [23.5 - 34.1 months] during HL and 20.5 months [18.7 - 72.2 months] (p: 0.14) (**Figure 2**).

#### 4. Comments

Among socio epidemiologic aspects, extranodal involvement is not uncommon, and some authors have published a frequency reaching 40% [2] [13]. This observation is also made in our study on patients who have comorbidities, especially



**Figure 2.** Overall patient survival according the type of lymphoma in Senegalese patients (p: 0.14).

diabetes and HIV, which may explain in part the extra nodal presentation [3]; which is comparable to the results found by Niang [14] in the same unit. In a large sub-Saharan multi-regional serie, a lower frequency (18.6%) of extranodal localization of the lymphoma could be linked to the inaccessibility of the radiological assessment [3]. In Africa, the diagnosis of extranodal lymphoma is made in patients in their fifties [3] [4], which is younger than the Western population [13]. There are no particularities of the age of onset of extra nodular lymphoma compared to the nodal form. Thus, our patients with HL were younger than those with NHL, consistent with data of lymphomas in sub-Saharan Africa [3].

Diagnosis was mainly suspected by the presence of suggestive signs, related to the location. At diagnosis, more than half of the patients had advanced deterioration and progressive symptoms of the disease, as described in the African series where patients traditionally consult late [3]. The main extranodal localizations were digestive, cutaneous, pleuropulmonary [1] [2] in our study. Although the authors agree that the digestive and cutaneous locations are the most frequent during extranodal involvement of lymphomas. The frequency varies for the different localizations in the different studies [15] [16]. Parotid, thyroid and breast involvement were rare [7]. Extranodal location was more frequent in primary (73.1%) than disseminated form of lymphoma (26.9%). However, the difficulty of clearly differentiating the primitive form or a secondary location remains a reality [2] [3] [4].

According to the subtype of lymphomas, the extranodal localizations of HL are less frequent, being around 5% to 15%, whether advanced stages or not [3] [17]. In our study, we observed only classic classic form of HL. On the other

hand, NHL can be up to 8 times more common, with a frequency around 30 to 40%. In this group of hemopathies, approximately one-third of patients with DLBCL present extranodal involvement regardless of the stage of the disease [1] [6] [7]. The preferred localizations of DLBCL are bones, bone marrow, nervous system and gastric [5]. MALT lymphoma is associated with gastric, but also thyroid and parotid locations [1].

Most of our patients were at an advanced stage (59.6%) and the prognosis was unfavorable in 56% (23 cases) above the value (46%) found By Alshemmari in Kuwait [7]. The high prevalence of adenopathy and the long time to diagnostic may explain this situation.

On biology aspects, anemia was the most common cytopenia seen in digestive involvement and was present in all patients with bone marrow involvement. This is a very frequent situation in lymphomatous pathologies. Its etiologies are multiple, can be central or peripheral, related to bone marrow infiltration, inflammatory and immunological phenomena, reduced intake and sometimes blood loss. They often combine, leading to a significant decrease in hemoglobin levels [18].

During the follow-up of our patients, around one-third reached CR. However, obtain CR in our setting is difficult due to the lack of diagnosis tools and access to drugs. We found a high prevalence of advanced stages like Mezger [3] who reported 78% in a multicentric sub-Saharan study. Therefore, the overall survival is shorter in associated extranodal lymphoma [7]. In our setting, the survival of patients followed for extranodal HL is better than that observed in patients with NHL, although this is not statistically significant. Survival remains low in our series of extranodal HL, because it is associated with poor prognostic factors. A better median survival of 34.2 months is reported in a Senegalese study that included observations of nodal and extranodal HL [19]. However, the survival profile is disparate with a better evolution in digestive MALT lymphoma (overall survival at 3 years: 5%) than in DLBCL (overall survival at 5 years in Ear Nose Throat: 45%) [5].

Limitations of the study are related to those of retrospective work responsible for the loss of documents, the unavailability of positron emission tomography to assess patients, and the lack of access to standardized treatment protocols. financed by the health authorities, in order to follow patients' survival.

## 5. Conclusion

Extranodal involvement of lymphomas is found in various sites, sometimes associated, and often diagnosed at advanced stages. Extranodal form of lymphoma, is frequent in B cell lymphoma, particularly DLBCL, it is also seen in T cell lymphoma. These lymphoma entities are particular in their aggressiveness and poor outcome, especially in our practice where the therapeutic options are limited.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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