Extranodal non-Hodgkin's lymphomas: a retrospective study

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Abstract

The involvement of extranodal sites is a common feature during the course of most non-Hodgkin lymphomas (NHL). However, some NHL emerge from different places other than the lymph nodes or spleen and are referred to as primary extranodal lymphoma (PE-NHL). The purpose of this study is to illustrate the clinicopathological features of patients presenting PE-NHL.

Among 125 patients studied with NHL, 37 cases (30%) were PE-NHL.

The ratio men/women was 1:1, with a mean age of 61 years old. There were 8 lymphomas (20%) of T-phenotype and 29 (80%) of B-phenotype. Skin and gastrointestinal tract were the most common sites, 32.4% and 29.7% respectively; 24% had B symptoms; 81% were localized (stage IE or IIE). Histologically (WHO classification), 3% of all cases had high aggressive features (Burkitt lymphoma), 68% aggressive and 29% indolent. Diffuse large B cell lymphoma (DLBCL) accounted for 51% and MALT lymphoma for 14% of all cases. According to International Prognostic Index (IPI), 7% of our patients were in the high risk group, 3% in the intermediate high, 20% in the intermediate low and 70% in the low risk group.

In conclusion, PE-NHL is a heterogeneous group of diseases, most of them localized in the skin and gastrointestinal tract. We found a higher percentage of T phenotype cases than those for nodal NHL. DLBCL was the most frequent histological subtype lymphoma. IPI was predictive of survival, but its use is uncertain on PE-NHL, because it can not stratify patients homogeneously.

Key-words: primary extranodal non-Hodgkin's lymphoma, skin, gastrointestinal tract, international prognostic index.

INTRODUCTION

Non-Hodgkin lymphomas (NHL) are the sixth most prevalence cancer in the world. Its incidence rate increased at 4% rate per year for the last 25 years of the 20th century, and practically doubled its incidence during such period.[1]

The extranodal commitment emerges frequently during the course of NHL. However around a third, are primarily originated in the extra nodal lymphoid tissue in the spleen.[2]

The definition of primary extra nodal NHL is controversial when one is before a simultaneous nodal and extranodal disease. At present, most authors[2] presume that a primary extranodal disease is defined in the presence of at least 75% of the tumoral extranodal volume with a clinical condition of dominant organ.

Some controversies remain: the definition of stage III and IV where is must be presumed as secondary nodal commitment and other organs as secondaries.

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Received for publication on the 23rd June 2010
Accepted for publication on the 22nd July 2010

There is no doubt that the chronic antigenic stimulus, and unregulated immune system, a genome instability, or the loss of control by the infection of oncogenic organisms, are important components in the etiology and pathogenesis of such entity.

The extranodal NHL distribution on different sites, changes according the institutions. Gastric location has been revealed consistently the predominant local, followed by the Waldeyer's ring or by the bowel and skin. More rarely, any organ of the human body can be a host for extra nodal NHL.[2-4]

The recurrences pattern in extra nodal NHL respects the concept of organotropism or homing, where the movements of lymphocytes circulation are made through similar lymphoid organs to those of origin. Such trend of re-circulating or recurring in extra nodal places is due to the molecules (integrins and selectins) complementary between the endothelium and the matching lymphocytes.[5]

OBJECTIVE

In the current work the authors review the frequency, the clinic pathological and immuno phenotypical characteristics of extranodal NHL in one single institution, contributing to the characterization of this Portuguese population. It was also evaluated the applicability of the clinical and prognostic index, the IPI.

TABLE I

Distribuição dos subtipos histológicos dos LNH-EP

	B Phenotype						T Phenotype				Total
	Diffuse Large Cells	Folicular	MALT	Marginal area	Mantle Cells	Burkitt	Gamma-Delta Hepato-splenic	S. Sezary	Anaplastic Large cells CD30+	Mycosis Fungoides	
GI T	5	–	5	–	1	1	–	–	–	–	11
Skin	4	–	–	1	–	–	–	1	3	3	12
Waldeyer	4	–	–	–	–	–	–	–	–	–	6
CNS	4	–	–	–	–	–	–	–	–	–	4
Bone	1	–	–	–	–	–	–	–	–	–	1
Liver	–	–	–	–	–	–	1	–	–	–	1
Gland salivar minor	–	1	–	–	–	–	–	–	–	–	1
Perinasal sinus	1	–	–	–	–	–	–	–	–	–	1
Total	19	1	5	1	2	1	1	1	3	3	37

Key: GI T: Gastrointestinal Tract; CNS: Central Nervous System; MALT: Mucosa associated lymphoid tissue.

MATERIAL AND METHODS

A retrospective study, by reviewing the clinical files of all patients with NHL diagnosis, with an age above 15 years, followed in appointments of the Oncology Service at Hospitals S. Marcos, from the 1st September 2006 to the 30th September 2008.

Nodal lymphomas were considered those affecting the ganglia, spleen and bone marrow. All other organs were perceived as extra nodal, including the Waldeyer's ring.

It was used to histologic classification of the World Health Organization, [6] Ann Arbor´s staging system with the risk stratification according to the International Prognostic Index – IPI .

The survival was calculated from the date of the diagnosis and the date of the patient's death; the groups assessed were compared using the test of Chi Square, with the Breslaw correction for small samples. The general survival was applied in the Kaplan-Meier curves.

125 cases of NHL were observed and were considered 37 cases (30%) as primary extra nodal.

RESULTS

On the 37 cases assessed, the average age was 61 years with a minimum of 21 and the maximum of 82, the ratio male/female was 1:1.the general survival was 78.6% at 24 months.

Only two patients (5%) had a primary commitment of two or more organs. As it can be seen on *Table 1* in 23 cases (62.1%) the initial manifestation was located on the skin and gastrointestinal system; 29 cases (78,4%) were B phenotype and 8 of T phenotype (21, 6%). The histological subtype more frequent was the DLC NHL (19 patients, 51.4%) followed by Malt Lymphoma (5 cases, 13.5%), Mycosis Fungoides (3 cases, 8.1%) and Anaplastic large-cell lymphoma CD 30+ (3 cases, 8.1%).

The search of *Helicobacter pylori* by the Gem son's method was negative in 4 out of 5 patients with gastric Malt lymphoma, as well as in the five patients with gastric ECS NHL.

According to the WHO histological classification, in our study 62.2% of NHL is aggressive, 35.1% indolent and 2.7% highly aggressive.

B phenotype is classified as aggressive (59.5%) and indolent (18. 9%); T phenotype is present in the remaining 21.6% of cases.

The clinical and laboratorial characteristics of our sample can be seen on *Table II*.

TABLE II

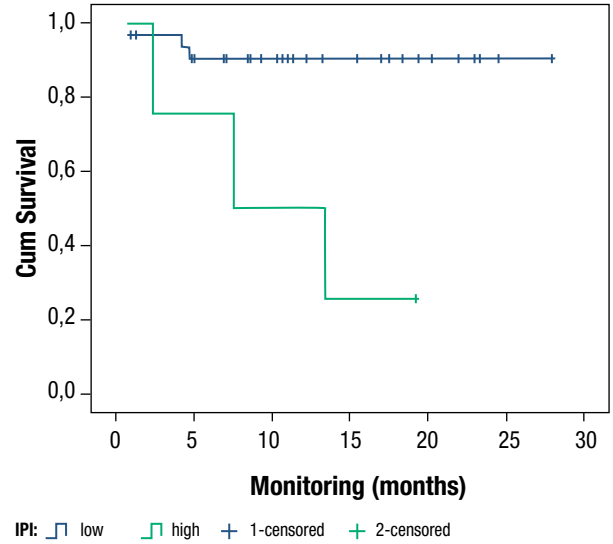
NHL-EP clinical-histological characteristics

	Nº cases (n/ %)	Survival 12 months (*p*)
Symptoms B		
Yes	9 (24,3)	53,3% (0,001)
No	28(75,7)	96,4 %
Affected local		
Skin	12 (32,4)	91,7% (0,92)
GI *	11 (29,7)	77,1%
Other	14 (37,9)	85,1%
Histological subtype		
DLCL	19 (51,4)	76,6% (0,514)
MALT	5 (13,5)	100%
Other	13 (35,1)	92,3%
Phenotype		
B	29 (78,4)	84,7% (0,497)
T	8 (21,6)	87,5%
Ann Arbor		
I, II	1 (2,7)	100% (0,308)
III, IV	23 (62,2)	76,1%
	13 (35,1)	100%
Ann Arbor		
I, II	30(81,1)	89,5 % (0,074)
III, IV	7 (18,9)	71,4%
LDH §		
Normal	30 (81,1)	96,4% (0,000)
High	7 (18,9)	42,9%
IPI		
0,1 e 2	33 (89,2)	90,5% (0,003)
3 e 4	4 (10,8)	50%

Key: GI: Gastrointesti; DLCL: Diffuse Large Cell Lymphoma; MALT: Mucosa Associated Lymphoid Tissue; LDH: Lactate dehydrogenase; IPI: International Prognostic Index.

It was compared the presence of B symptoms in groups of located diseases (stages I and II) and widespread diseases (stages III and IV), and it was found a significant statistical association ($p < 0.005$) between the presence of the symptoms and the group with widespread disease.

Seven patients (18.9%) had high levels of LDH at the time of the diagnosis; three of these patients belong to the low risk IPI group and four belonging to the high risk IPI group.



Survival curves in IPI group patients (low risk vs high risk).

FIG. 1

Patients with high LDH present an average survival of nine months and the reminder (normal LDH) 27 months. It was demonstrated a correlation with statistical significance ($p > 0.05$) between high LDH and the patients survival.

Those with a located disease (stages I and II) have presented a mean survival of 25 months; and those in advanced disease 14 months. It seems therefore to exist a trend to a longer survival in the earlier stages although it does not reach differences with statistical significance ($p = 0.074$).

Patients belonging to the lower risk group and low intermediate (IPI I and II) present a statistically significant difference ($p = 0.003$) in your overall survival regarding patients with a high intermediary and high risk (IPI III and IV). The mean survival of the low and high risk groups were respectively between 25 months and 10 months (*Fig. 1*).

31 patients were still alive at the end of this study; six patients (16.2%) died. Among these, two patients were carriers of anaplastic large-cell gastric diffuse NHL; one patient had Sezary syndrome, another diffuse cutaneous large-cell NHL in the thigh, and another one NHL in the nervous central system and lastly the Gamma Delta hepatic splenic NHL T. The average period of following-up was 11 months.

DISCUSSION

Extranodal NHL are around 1/3 of all NHL, being the number of the former increasing, in the last decade, due to limit improvement on the complementary means of diagnosis and to a more careful filing of the existing data. The can be present in any organ, with preferential incidence in the gastrointestinal tract, Waldeyer's ring, [7] skin and bones. [4]

In our study, the 37 cases (30%) of extranodal NHL have an incidence similar to the one described in literature. Most cases presented themselves in the skin, followed by the gastrointestinal tract and the Waldeyer's ring.

It's not totally known the reason why some organs are more affected than others; however it has been suggested an antigenic stimulation in unregulated immune system contributes to the primary extranodal NHL pathogenesis. Therefore the most affected organs like auto immune diseases or by chronic infection (as the *Helicobacter pylori*) can be more subject to NHL occurrence.

Regardless of the general distribution of multi--institutions, it was described the influence of the experience in the center of the frequency of the extra nodal LNH found. In the current study for instances, the most frequent lymphomas were those of cutaneous origin because the hospital has a main Dermatology service.

There are clinical and biological differences between the nodal and extranodal NHL. For instances, the extranodal have a higher incidence in older people and the ratio male-female is less than one. In our study the average age was 61 and the ratio male--female was one.

The symptoms are rare and our study was not an exception, with an incidence of 24%.

Primary cutaneous NHL are, most of them, T phenotype, becoming the mycosis fungoides and Sezary´s syndrome 65% of cases in this study. In cutaneous NHL of B phenotype there is a predominance of DLC of the head and trunk with an indolent clinical behavior. However, the subtype DLC in the leg is very aggressive and in our study the only case became fatal.

In our study the T phenotype has a 21.6% incidence theoretically higher-than-expected, justified by the great incidence of cutaneous NHL.

Regarding the gastrointestinal primary NHL it is known that 50 to 60% are gastric, 30% of the small bowel and 10% of the colon. DLC NHL are the most common subtype of gastric NHL, and some result of transforming the NHL marginal area. Gastric Malt NHL emerge more often in people above 40 years of age.

There is an etiological correlation between NHL Malt gastric and infection by *H. pylori*.[8] For reasons we do not know about 4 out of our 5 cases of NHL Malt gastric were negative for *H.pylori* research, as well as all other high grade gastric NHLs.

In general, the most common histological subtype was the diffuse large cells NHL (51.4%) followed by the Malt NHL (13.5%), agreeing with some studies.[9] The histological variations found in the extra nodal NHL include not only those presented by nodal NHL as their own variations.

Therefore that DLG NHL (which can emerge in any location but it is very frequent in testicles and the CNS), the extrafolicular NHL and the mantle cell NHL (the latter frequent in the digestive tract) are common both to the nodal and extra nodal NHL.

But the NHL on the marginal area of the lymphoid tissue associated to mucosa (MALT), another variation, the intestinal marginal lymphoma called lymphoproliferative disorder of the small bowel, also called Mediterranean or heavy chains lymphoma, the intestinal T-cell lymphoma, enterohepatic type, and the NK/T lymphoma, nasal type, emerge exclusively in extranodal tissues.

The hematologic classification of neoplasms for the World Health Organization defines neoplasms in B-cells, T-cells and *Natural Killer* cells. The importance of such histological classification resides in the clinical behavior (indolent, aggressive, very aggressive) of the NHL in question. Indolent NHL (Centro follicular, marginal area including Malt, mycosis fungoides) have a longer survival even without treatment; aggressive and highly aggressive NHL are curable but are quickly fatal if they are not treated or are resilient. In our study it was not possible to establish the relationship between the survivals on 12 months in indolent NHL when compared with the aggressive ones. In the highly aggressive NHL group (L.Burkitt) there was only one case remaining alive and without disease until the end of the study.

Those with a localized disease had a higher survival in relation to the widespread disease, however it was not possible to establish a statistically significant correlation. Such finding seems relevant to us and this might not be at all unexpected: Ann Arbor staging

system was created to stratify patients with Hodgkin's Lymphoma; this, on the contrary of the NHL evolves and progresses on sequel platforms, reaching the nodal chains from one pathologic ganglion.

Regarding the NHL biology, the process is distinct, with possible extra nodal disease or affecting the bone marrow in spite of the scarce nodal tumoral mass. Such fact translates an insufficient correlation between the tumoral mass and the evolution platform, measured by the Ann Arbor system in the case of NHL. The discriminatory inability of such system to measure the tumoral mass and the prognosis led to the emergence of the IPI, specifically adapted to high grade NHL. Subsequently emerged both the FLIPI and the MIPI adapted to the follicular and the mantle cell lymphoma, respectively.

In this work it was confirmed that Ann Arbor system is not useful for extranodal NHL.

A statistically significant correlation was shown to exist in patients with high LDH and high grade IPI, being associated with a higher mortality. The clinical usefulness of IPI in extranodal NHL raises however some difficulty, as it badly stratifies patients; most of them belonging to the low risk group and only 10% were in the high risk group, where it can be predicted a more aggressive evolution.

Once that our study is retrospective and it has a small sample, conclusions must be taken with precaution. It will be necessary an increase on the studying sample and/or the conjugation with data from other centers to establish premises with a more powerful statistical meaning.

CONCLUSION

Cutaneous and gastrointestinal tract lymphomas have demonstrated to be the most prevalent, as well as the histological subtype of diffuse large cells NHL.

The IPI has demonstrated to be a discriminatory factor in the patient survival, but it does not stratify patients in homogenous groups and therefore its use is doubtful on extranodal NHL. ■

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