CLINICAL AND HISTOPHENOTYPIC ASPECTS IN PERIPHERAL T LYMPHOMAS ON A GROUP OF 197 PATIENTS FROM BUCHAREST

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Abstract: *T lymphoma diagnosis can be established only by immunohistochemistry and immunophenotyping. This requires well equiped laboratories and not least a specialized dedicated personnel. There are few centers in the country where phenotyping is currently performed. There is no national registry of patients with peripheral T-NHL and we consider that this represents a necessity in order to achieve a clear record of the patient (from diagnosis until the end of the disease) for a more accurate classification of cases based on prognostic factors and a more targeted therapy for a greater survival. We studied 197 patients with Lymphoma T Fundeni and corner for a period of eight years (2000-2007), the present 25 cases of lymphoblastic lymphoma and 172 cases of peripheral T lymphomas. The incidence was almost similar to literature data and batch characterization overlapped broadly on T lymphoma profile outlined in the literature*

Cuvinte cheie: *PTCL, tratament, imunoterapie*

Rezumat: *Diagnosticul limfoamelor T nu se poate stabili decât prin imunohistochimie şi imunofenotipare. Pentru aceasta este nevoie de laboratoare dotate cu reactivi şi aparatură şi nu în ultimul rând de personal specializat şi cu dăruire. Sunt puţine centre în ţară în prezent unde se face fenotipare. Nu există un registru naţional al pacienţilor cu LMNH T periferice şi considerăm necesar realizarea acestuia pentru o evidenţă clară a pacienţilor (de la diagnostic până la sfârşitul evoluţiei bolii) pentru o încadrare mai corectă a cazurilor în funcţie de factorii de prognostic şi o abordare mai ţintită terapeutică pentru o supravieţuire mai mare. Am studiat 197 pacienţi cu Limfoame T din Fundeni şi Colţea pe o perioadă de 8 ani (2000-2007), fiind prezente 25 cazuri de limfoame limfoblastice şi 172 cazuri de limfoame T periferice. Incidenţa a fost aproape similară cu datele din literatură iar caracterizarea lotului s-a suprapus în linii mari pe profilul limfoamelor T conturat în datele din literatură.*

THE AIM OF THE STUDY

The aim of the study is to identify clinical and histophenotypic parameters with prognostic value using as a study instrument the observation sheet, histopathologic and immunophenotypic bulletins of patients with T-NHL. We also intend to study the expression of cellular and molecular biomarkers to highlight their predictive value.

We want to group the parameters into favorable and unfavorable after the study conducted. We will also analyze in dynamic clinical, histophenotypic aspects and response to treatment based on regimens used, in order to identify treatment regimens with optimal effect on survival and quality of life..

MATERIAL AND METHOD

Our study is a longitudinal one with a retrospective component following patients admitted in Hematology Clinics of Clinical Institute Fundeni and Clinical Hospital Coltea, between 2000 and 2005 (6 years) and a prospective one 2006-2008 (3 years), mentioning that in the prospective group are included only a part of cases diagnosed until 2007. The inclusion criteria were based on the demonstration of T phenotype of patients through biopsy with immunohistochemistry or flowcytometry.

There were included 228 cases of T NHL from Clinical Institute Fundeni and 229 cases from Victor Babes Institute. Some were pediatric cases or from other hospitals in the country and in Bucharest so our group finally consisted of 197 T lymphoma

RESULTS

In analyzing the results we took into account the WHO classification of lymphomas**.**

CLINICAL AND BIOLOGICAL CHARACTERISTIC OF PERIPHERAL T LYMPHOMAS GROUP

Our group consisted of 197 T lymphomas: 153 from Fundeni, 44 from Colţea. Of these, 25 were lymphoblastic T lymphoma (12%) and 172 peripheral T lymphoma (peripheral T-NHL 88%). Of the 172 cases of peripheral T-NHL, 43 came from Coltea and 129 from Fundeni. There were 142 new cases of NHL out of 1462 patients with T and B NHL hospitalized in Fundeni from 2000 to 2006, which means 9.7 percent compared to 12% as described in the literature, with variations of 10% in the Western countries and 80% in Japan and Taiwan due to the increased incidence of HTLV. The incidence was higher in 2004 (13.9%) and 2005 (12.3%) similar to the known incidence, being lower in 2001 (4.8%) and 2006 (7.8%). There were 122 peripheral T-NHL in those seven years, representing 8.3% versus 10% as described in the literature. The incidence of peripheral T lymphoma cases per year is superimposable on that of T-NHL in general, greater in 2004 and 2005 of 12% and respectively 10,3%, probably due to the increase of diagnostic methods and of immunophenotyping for a more complet and accurate diagnosis, but does not explain the decline from 2006.

Analyzing the demographic, clinical, biochemical, hematological characteristics of the group we found that, as expected, 82 patients were from Bucharest (47%) and 90 from other counties.

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Table No.1 Distribution of the patients with T-NHL and its subtypes according to WHO classification by years

Classification of patients on disease subtypes and years	Number of patients 2000	2001	2002	2003	2004	2005	2006	2007
T and B NHL (1462pt/7years-1650/8years) dg in Fundeni	224	183	232	176	215	202	230	188
T NHL studied group in Fundeni &Coltea: (197p/8years)	24	11	25	21	39	32	31	13
T NHL Fundeni (142p/7years;151p/8years) I=9,7%	23 10,2%	9 4,8%	20 8,6%	17 9,6%	30 13,9%	25 12,3%	18 7,8%	9
1.Lymphoblastic T NHL (25 pt) i=1,6%NHL T and B i=12% NHL T studied group	4	2	2	4	4	4	3	2
2.Peripheral T NHL (172 pt) i=88% studied group	20	9	23	17	35	28	28	11
Peripheral T NHL Coltea (43p)	1	0	5	4	9	7	13	4
Peripheral T NHL Fundeni (122p/7years,128p/8years)I=8,3%	19 8,9%	9 4,8%	18 7,7%	13 7,3%	26 12%	21 10,3%	15 6,5%	7
I.DISSEMINATEDF/ LEUKEMIC PRED	1	2	6	0	3	3	5	1
II.NODAL PREDOMINANCE	24	15	15	19	34	24	26	13
III.EXTRANODAL PRED	1	0	3	3	6	5	1	2

Table no 2 Features of T NHL group

	Age (years) ≤ 60	> 60	Sex M	F	Environment U	R	ECOG PS 0-1	2-4	Systemic symptoms	Stage Ann Arbor I-II	III-IV	Bulky disease
Patients no	114	42	108	64	131	41	102	54	133	27	132	23
Percent	73	26,9	62,7	37,3	76,1	23,9	65,3	44,7	77,3	26,99	83	14,6

	Bone marrow involvement	Abnormal LDH	Extranodal determination 0	1	>2	IPI 0, 1	2	3	4, 5
Patients no	**72**	**106**	**68**	**87**	**2**	26	43	58	31
Percent	**45,5**	**67,08**	**43,3**	**55,4**	**1,2**	16,4	27,2	36,7	19,2

	Cutaneous det	Oseous det	Hepato megaly	Pulmonary det	Spleno megaly	CNS involvement	supra diafragm adenop	sub diafragm adenop
Pts no	39	25	81	9	63	15	120	71
Percent	27,6	17,7	57	6,3	57,4	10,6	76,9	45,2

In the studied group, ¾ meaning 131 patients came from urban area, 41 from rural area, possibly because of better addressability to physician and better information of patients from cities. Two thirds of the patients were men (108 cases) and 64 women, in the literature male sex being predominant for this type of lymphoma.The mean age of peripheral T-NHL group was 49.9 years (with a minimum of 16 years and a maximum of 91 years), lymphoblastic lymphoma group being younger with a mean age of 30.7 years. Most studies have used the IPI (international prognostic index) for the prognosis assessment which is based on clinical and laboratory criteria and has proven validity in diffuse large B cell lymphoma and has proved accurate also in determining the prognosis, survival prediction in other lymphomas. There are followed 5 parameters, giving one point for: patients over 60 years, ECOG performance status of 2-4, Ann Arbor stage III-IV, presence of over 2 extranodal determinations, abnormal LDH values. IPI score is then determined and the patients are fit as having good prognostic factors- IPI score 0 and 1, intermediate-good prognostic factors - score IPI2, intermediate-poor- IPI score 3, poor-IPI score 4 and 5. Thereby we noticed that in our group over 50% of patients presented a good performance status (ECOG) at diagnosis. Unfortunately 83% of them presented advanced stages of disease (stage Ann Arbor III and IV), which darkens the prognosis and response to treatment and decreases survival. Over ¾ of patients (77%) presented B signs of disease (fever > 38 degree C, sweating, weight loss) at presentation which explains in part the faster presentation to physician and the shorter duration compared with other hematologic malignancies. Unlike lymphoblastic lymphomas only 14.6% of patients had bulky disease. With a highly statistical significance 67% of patients had higher than normal LDH. 56,6% of patients had extranodal determinations. Extranodal sites involved: bone marrow, liver, spleen, skin, Waldeyer ring, lung, pleura, bone, mucosa, soft tissue, brain. From the analysis of these data we found an IPI of 0 and 1 in 26 patients, IPI 3- in 58 people and IPI 2- in 43 people. A not insignificant number of 31 people (almost 20% of cases) had IPI 4. Mean value of LDH in studied group was 859 u/l.

Only nine patients experienced bleeding syndrome at diagnosis, 42 patients had anemia syndrome, among which 12 were severely anemic. The mean value of leukocytes in our group was 14744/mm3 and of lymphocytes 8846/mm3. When lymphoid elements were detected in periphery, they have fluctuated between 31 and 72%.

The mean calcium was 10.5 mg / dl with a maximum of 22, all these high values being explained by inclusion in the group of cases of adult T-cell lymphoma / leukemia HTLV-positive which, as it is known, may present at any point of evolution metabolic coma at which contributes also the hypercalcemic one. Mean transaminases levels were 79mg/dl for TGO and 74mg/dl for TGP which shows frequent liver involvement (57%). Splenomegaly was present at 57% patients. Beta 2 microglobulin, a marker essential to follow in lymphoproliferations both at diagnosis and in disease evolution and also in relapses, was determined only in 14 people, 10 of them having elevated values.

HBS antigen was positive at 5 patients, 9 patients had positive anti HVC antibodies, 2 cases HIV positive, 23 cases had positive anti HTLV antibodies: all the 17 ATLL cases, 1 case of mycosis fungoides, 1 case of anaplastic lymphoma, 1 case of peripheral T large cell NHL, 1 case of peripheral medium T cell, 1 case of T cell with nasal determination, 1 case of nonspecific peripheral T small cell. From our group 41 patients had cutaneous determination, 28 bone determinations, 10 pulmonary determinations, 15 CNS damage. Thereby it is confirmed that unlike other lymphoproliferations in nonhodgkin lymphomas extranodal involvement is more common, especially in T lymphoproliferations.

In our group of patients were performed 139 immunohistochemistry, 35 immunophenotyping (mostly in peripheral blood but also in bone marrow, spleen cell suspensions). In 91 patients immunohistochemistry was applied on lymph nodes, in the other cases on tonsils, cavum tissue or from nasal tumor, skin, bone marrow, stomach, intestine, liver, spleen, kidney, femur, thyroid, mediastinal tumor, orbital tumor, vertebral, paravertebral, pulmonary, extradural, retroperitoneal tumor. 20 patients received both tests immunohistochemistry and immunophenotyping. 87% of patients see a doctor within the first six months from the onset of first symptoms, most patients in the first month – 51 patients.

Adult T-cell lymphoma / leukemia-ATLL accounted for 9.8% of peripheral T lymphomas. According to ATLL classification: 10 were chronic forms, 6 acute forms and one lymphomatous form. The ***evolution*** was in some cases with hypercalcemic, hypernatremic metabolic coma, hepatic encephalopathy, and cerebral hemorrhage. It was the group with the highest number of deaths 83%. **Anaplastic lymphoma** is T-NHL subtype which represents number 2 in frequency after non-specific peripheral T cell NHL: 44 cases from 172 cases of peripheral T-NHL (24%). From those 44 cases 16 are anaplastic null and 29 anaplastic T. It is one of the lymphomas with greater diagnosis difficulties before immunohistochemistry achievement. Thus, in our group, diagnosis as Hodgkin's disease, undifferentiated carcinoma, timoma, immunoblastic lymphoma, follicular lymphoma, reactive lymphadenitis were established for patients with ALCL before completion of IHC. ALK has been performed in 30 cases being positive in 15 cases. It is the subtype of T NHL with most cases with low risk and low intermediate risk which overlaps with the literature data demonstrating better survival and better response to treatment. **Angioimmunoblastic lymphoma** represented by 9 cases has a mean age greater than T lymphomas group, of 59 years. Anamnesis found exposure to roentgen rays, plastics and silicon oxide. **Mycosis Fungoides/ Sezary Syndrome**: 10 cases, 6 cases having Mycosis fungoides and 4 Sezary Syndrome (immunophenotyping was performed for these because it is known that they experience peripheral Sezary cells download), probably most cases being treated in dermatology services in the country. Until the correct diagnosis establishment the patients were labeled as having parapsoriasis vulgaris, chronic allergic dermatitis, contact dermatitis. **Lymphoma/leukemia with large granular and NK cells,** present with 6 cases, is the only entity in which we found the predominance of female sex. **T cell NHL with hepato-splenic determination** Although only 16 cases were described in the literature we had in studied group 2 patients with hepatosplenic T cell NHL and a 19 year old patient with T cell NHL / NK TCR gamma delta with hepatosplenic determination who also had celiac disease and thymic determination. **Intestinal T cell NHL** was represented by three cases with onset symptoms of abdominal pain, weight loss, faeces peritonitis. **NHL with nasal determination** was present in 3 patients. **Nonspecific peripheral T-NHL** is the most representative subset with the highest frequency -75 patients-41% of peripheral T lymphoma group with an incidence in Fundeni of 3.4% of all B and T lymphomas vs. 3,7% as described in the literature. 5 cases of lymphoepitheloid lymphoma Lenert were present, 24 patients with large cell, 16 with medium cell, 30 with small cell..

DISCUSSIONS

Among the 197 analyzed cases of T lymphomas, 25 are lymphoblastic lymphoma, 172 peripheral T cell lymphoma, the latter having a frequency close to that of literature, greater in 2004 (12%) and 2005 (10.3%). It predominates ***nonspecific peripheral T lymphomas*** with an incidence of 3,4% in Fundeni of all T and B lymphomas vs. 3,7% as described in the literature. This includes 5 cases of lymphoepitheloid lymphoma Lenert. Next in frequency is systemic anaplastic lymphoma with a total of 44 cases (24%). ***Adult T cell Lymphoma /leukemia*** are on 3rd place with a total of 17 cases (9.8%). The three types of lymphoma represent about **75%**, the remaining subtypes occur with a much lower frequency: 9 cases of angioimmunoblastic lymphoma, 6 LGL type lymphoma and one with NK cell, the rest are predominantly extranodal lymphomas. Although very rare in frequency in the literature, we found three nasal T cell lymphomas, 2 cases with hepatosplenic determination and one case of T cell / NK TCR γδ (only 16 cases described in the literature) which presented also celiac disease. Cases of MF / SS are much lower than in literature, the majority being treated in dermatology departments. It is possible that the number of cases of T NHL will be underestimated because in our country not all lymphomas benefit from IHC and on the other hand it is needed an experienced pathologist, specialized in hematologic malignancies. It is known that T NHL has a much more dramatic evolution and needs much more aggressive treatment regimens than B lymphomas which require a correct diagnosis, clinical and immunohistochemical, from the beginning.

Even so, there are sometimes diagnosis difficulties, cited also in the literature, in our study most incorrect diagnoses being assigned specifically for anaplastic lymphoma (often being confused with Hodgkin's disease). Addressability to the doctor was higher in the first month of symptoms' onset probably due to the aggressiveness of the disease, mostly being with systemic symptoms, advanced disease stage III-IV, peripheral lymph nodes. The disease predominates in young people, coming mostly from urban areas, probably due to greater exposure to toxic substances, higher addressability to the doctor because of better information, and easier access to medical service and even due to travel opportunities in countries with endemy for HTLV. According to the literature the disease affects 62.7 percent of males the single exception being LGL / NK lymphoma. Bone marrow involvement was 45.5%, LDH higher than normal in 67% patients and 56% extranodal determination, which are important prognostic variables. Most patients were classified as high intermediate risk group, then as low intermediate. A not insignificant percentage in view of the extremely short survival and response to treatment was that of high-risk patients (19.2%). A significant percentage of patients had skin, neurological and other determinations showing that extranodal involvement is greater than in B lymphomas. Most determinations were neurological in patients with ATLL, usually through metabolic coma but also through brain hemorrhage and lymphomatous infiltration. A large number of viral infections raise the question of their involvement in disease pathogenesis. There were no many bleeding syndromes and only 42 patients had anemia syndrome. Histology, immunophenotyping and immunohistochemistry was superimposed on the data from the literature, but for anaplastic lymphoma which has the longest survival, the best answer to

treatment, especially if the cases are ALK +, we have not found significant differences between anaplastic NHL ALK + and ALK-. Unfortunately there was only one cytogenetic determination for our group, one t (2, 5) specific for anaplastic lymphoma and no molecular determination. When biochemical markers Ki67, bcl2, PCNA were investigated, they decreased prognosis and survival.

CONCLUSIONS

T lymphoma diagnosis can be established only by immunohistochemistry and immunophenotyping. Further cytogenetic and molecular biology investigations would be necessary for a complete diagnosis. There are few centers in the country where phenotyping is currently performed. There is no national registry of patients with peripheral T-NHL and we consider that this represents a necessity in order to achieve a clear record of the patient (from diagnosis until the end of the disease) for a more accurate classification of cases based on prognostic factors and a more targeted therapy for a greater survival. We studied 197 patients with T Lymphoma from Fundeni and Coltea for a period of eight years (2000-2007), 25 cases being lymphoblastic lymphoma and 172 cases peripheral T lymphoma. The incidence was almost similar with that from the literature and group characterization overlapped broadly on the profile of T lymphoma outlined in the literature. A final conclusion is premature to assess, the group being incomplete and the correlation of each factor to survival and response to treatment is absolutely necessary for reliable conclusions..

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