

PERIPHERAL T LYMPHOMAS. CLINICAL AND HISTOPHENOTYPIC ASPECTS IN PERIPHERAL T LYMPHOMAS

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Abstract: Nonhodgkin malignant lymphomas (NHL) represent a heterogeneous group of immune system cells- monoclonal tumors (lymphocytes and histiocytes). NHL can be divided phenotypically in T cell lymphomas and B cell lymphomas. T cell NHL are recognized only by three decades. They have an incidence of 12-15% and represent a heterogeneous group from clinical, evolutionary and histophenotypic point of view, which raises many problems of diagnosis and therapy.

Cuvinte cheie: LMNH T, clinica LMNH, histologia LMNH, fenotipare LMNH

Rezumat: Limfoamele maligne nonhodgkin (LMNH) reprezintă un grup heterogen de tumori monoclonale al celulelor sistemului imunitar (limfocite și histiocite). LMNH se împart din punct de vedere fenotipic în limfoame de tip T și de tip B. LMNH de tip T sunt recunoscute doar de 3 decenii. Au o incidență de 12-15% și reprezintă un grup heterogen din punct de vedere clinic, evolutiv și histofenotipic ceea ce ridică numeroase probleme de diagnostic și de conduită terapeutică.

T NHL represents a malignant proliferation of T cell with a wide clinical and pathological spectrum. WHO classification (1,2,3) divides T-cell NHL in precursor T (T lymphoblastic lymphoma) and peripheral T cell lymphomas (peripheral T-NHL). The last are the subject of our study and in turn are classified by the predominant form of clinical manifestation:

1. **Leukemic / disseminated type with subtypes** with subtypes a) Prolymphocytic T leukemia; b) lymphoma/leukemia with large grain cell (LGL); c) NK cell leukemia; d) lymphoma / adult leukemia with T-cell (ATLL), HTLV positive
2. **Nodal predominance type** with subtypes: a) T cell NHL with angioimmunoblastic T cell (LAI); b) non-specific peripheral T cell NHL (PTCL US); c) NHL with large anaplastic T cell type or null systemic type (ALCLs)
3. **Extranodal predominance type** with a) anaplastic T NHL or null primitive cutaneous NHL (ALCLc); b) Mucosis fungoides / Sezary syndrome (MF / SS); c) Extranodal T NHL / NK nasal type; d) T cell NHL with enteropathy; e) T cell NHL hepatosplenic type; f) subcutaneous panniculitis.

NHL T frequency is in average 12% of NHL ranging from 1.5% in Canada, Vancouver, British Columbia to 18.3% in Hong Kong. This variation is given by the higher incidence in Asian countries with HTLV infection and Epstein-Barr virus. (4,5) T lymphoproliferations can occur also in the evolution of patients with known B NHL, Hodgkin's disease, Sjogren's syndrome, Hashimoto's thyroiditis, ITP, celiac disease, rheumatoid arthritis. Each subtype of peripheral T-NHL shows specific clinical, morphological, histophenotypic, genetic and molecular features. There are also some general characteristics of T lymphomas: occurring in middle-aged adults or older adults with disseminated disease at diagnosis (68% cases), with systemic symptoms in almost half the cases, bone marrow involvement in 25% of cases, extranodal in 1 / 3 cases. They

have poor prognosis despite aggressive therapies performed, half of patients passing away through disease progression. (6,7,8) T phenotype per se give to disease an aggressive course.

Nonspecific peripheral T-cell NHL - PTCLUS appears with a frequency of 3.7% of all NHL. (8,9).

It represents one of widespread T lymphomas in North America, a heterogeneous group with multiple morphological subtypes, heterogeneous clinic, distinct biology, not known prognostic significance., with 5-year survival of 30-35%. Most patients have positive nodes but also extranodal involvement in the liver, bone marrow, gastrointestinal tract, skin. Lymphoid elements from lymphatic nodes express CD4+, CD8+, CD30+. *Morphologically* there is a mixture of inflammatory neoplastic cells including plasma cells, eosinophils, epitheloid cells. Malignant cell cytoplasm is moderate or rich, pale and nucleus is cleaved or convoluted. Vascularization is usually increased.

NHL with large anaplastic cell -ALCL

It represents approximately 2,4% of all NHL.(9) Morphological is characterized by a high pleomorfism, anaplastic large cell invasion of lymphatic nodes sinuses with abundant pale cytoplasm, nucleus with single or multiple nucleoli, pleomorf or horseshoe-like. *Immunophenotypical it express uniformly* CD30+(Ki-1), most have EMA +. *Cytogenetic:* In 1994 Morrison revealed t (2, 5) and the pathogenic importance of gene ALK (anaplastic lymphoma kinase) in ALCL. It is divided into cutaneous and systemic ALCL. Systemic ALCL may be with T or null cell. It has the highest survival in the NHL type T, somewhat similar to diffuse large B-cell NHL. 5-year survival is 93%. Systemic ALCL are ALK + in 60% cases. *ALCL ALK + patients* are young, have systemic disease, wide spectrum morphology which ranges from small cell (over 75%) to large cell (30%), pleomorphic and 70% monomorphic, EMA positive, positive cytotoxic protein. ALCL ALK- patients are usually: older people with advanced disease stages, increased LDH, B symptoms of disease, extranodal involvement having a lower clinic and survival similar to the PTCL US. Cutaneous ALCL are a distinct entity with primary

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CLINICAL ASPECTS

cutaneous disease in the absence of systemic involvement, with indolent evolution and increased survival. (9,10,11,12,13,14)

T cell and NK extranodal NHL – nasal type

It represents approximately 1,4% of all NHL.(9) It is the entity that has a racial and geographical distribution, being unusual in the western population. It is characterized from a morphological point of view by vascular destruction, angiocentric invasion, necrosis. Epstein Barr virus is incriminated in their pathogenesis. They have type NK / T phenotype: CD2-, CD56 +, CD3cy + EBV + and rare cases with clinical features and patterns of cytotoxic T lymphocyte, CD56-, EBV +. Location is usually limited to upper respiratory tract, nasal cavity and palate, causing necrotic and ulcerative lesions, nasal septum perforation. **NHL T/NK systemic type** It is extremely aggressive, survival at 5 years being 20-35%.(15)

Lymphoma/leukemia with large grain cell LGL

It is a proliferation of T gamma lymphocytes or T8 lymphocytes associated with neutropenia which can be as suppressor T lymphocyte phenotype (CD2, CD3, CD8) or NK cells phenotype (CD2, CD56, CD57); it occurs in men with discrete hepatosplenomegaly without nodal or cutaneous disease, with leukocytosis and lymphocytosis, moderate anemia and neutropenia. It occurs frequently after a history of rheumatoid disease.(16) Morphological lymphocytes are medium or large, with small kidney-shaped nucleus, condensed, large cytoplasm with asuophilic granulations, in which is found acid phosphatase and beta-glucuronidase. Neutropenia is severe in 50% of patients, less than 500 granulocytes / mmc, Coombs test negative, bone marrow infiltration with lymphoid elements by 30-70%, erythropoietic and granulopoietic series may be normal or reduced (up to erythroblastopenia). (17)

Angioimmunoblastic NHL

It represents approximately 1,2% from all NHL.(9) It is described as an atypical reactive process in patients with lymphadenopathy, rash, hepatosplenomegaly, fever, hypergammaglobulinemia or disproteinemia, but cytogenetic and molecular studies confirm clonality in most cases; sometimes is associated with autoimmune haemolysis. It is characterized morphologically by the increased vascularization, arborization type, post capillary venules are hyalinized, forked by plasma cells and large atypical cells have pale cytoplasm and may be scattered among the other cells or on the contrary gathered in nests. They have CD21 expression on dendritic follicular cells and identification of CD10 + as a phenotypic marker on neoplastic T cells. Movers point for pathogenesis may be infection of B cells with with Epstein Barr virus, monoclonal or oligoclonal type. Patient prognosis is poor; survival at 3 years is 30%. Vascular proliferation and presence of immunoblasts explains the name angioimmunoblastic.(18,19)

T NHL with intestinal involvement

It is a subtype of lymphoma that can complicate or unmask sensitivity to gluten. Sometimes occurs in the absence of a known history of celiac disease, but histopathological are present vilous atrophy and glandular hyperplasia of the intestinal crypts. Jejunum is the most common location of gastrointestinal lymphoma. *Clinical*, older men are affected more commonly who present with abdominal pain, diarrhea, steatorrhea, digital hypocratism, hypoproteinemic edema, symptoms of vitamin A deficiency (follicular hyperkeratosis, hemeralopia, dry eyes), vitamin B1 deficiency (neuritis Beri-Beri), vitamin B2, B12, folate, iron deficiency (cheilitis, stomatitis, glossitis, megaloblastic anemia), vitamin K deficiency (bleeding syndrome). It is known that 10-15% of patients with gluten enteropathy develop malignancies, intestinal lymphoma representing 50% of malignancies which appear in gluten enteropathy. Phenotypic profile is CD3 +, CD7 +, CD4-, CD2 +

and usually CD8. The survival of these patients is poor, due to complications which evolve with malnutrition, however the highest risk is that of intestinal perforation.(20)

Adult T cell lymphoma/leukemia –ATLL

The cause is HTLV infection, almost two thirds of patients are diagnosed at stage 3 or 4, the incidence is higher in endemic territories: the Caribbean Basin, southwest Japan, but isolated cases of disease can occur in non-endemic areas at persons who have traveled or coming from endemic areas. Only 1 in 2000 infected people have the disease. Latency period from infection until the disease is manifest can be as high as 30 years. Proportion of illness reaches 30% in Japan, 6% in the Caribbean, 1% in the U.S. Most are *phenotypically* CD4 +, CD8-CD25 + and are negative for CD7. The disease occurs more frequent in adults, the prevalence of male / female 1,5 /1. *Clinical* they can be divided into acute type (leukemic), lymphomatous type, chronic and smoldering. Acute type has a rapid progression to exitus. It is characterized by skin rash-erythrodermia, skin tumors, hepatosplenomegaly, B signs of disease, pulmonary infiltration, lithic bone lesions, hypercalcemia, leukocytosis by the presence of atypical lymphoid elements. *Morphological* cells have cleaved, incised nucleus, lobulated aspect of clover. Histologically skin involvement is dermal. Lymph node involvement spare partially the architecture, with follicles present, often reactive; in dependent T zone infiltration with atypical cells and hyperplasia of post capillary venules are observed. Death occurs by infection, hepato-renal failure. The other forms are rarer and can develop into acute form.(4,5,21)

Hepatosplenic NHL with gamma/delta T cell

It was described for the first time in 1990; 50 cases were described until now. Most patients are young, around 34 years old. Clinical shows hepatosplenomegaly, abdominal pain, B signs of disease, without adenopathy. They may have bone marrow involvement. There can be meet with a low rate myeloid precursors, hemophagocytic syndrome; often have anemia and thrombocytopenia, hepatosplenic and bone marrow sinusoidal infiltration with small or medium monomorphous cells that express TCR gamma / delta. *Flow cytometry* : CD2+,CD3+,CD5-,CD7+/-,CD16 +/-, CD56+CD4-, CD8-, CD20-, TCR, gama/delta +. *Immunohistochemistry* CD5-, CD3+, CD56+, p53-, bcl 2 -,Tia 1+, granzim B-. Average *survival* is 16 months by disease progression.(22,23,24,25)

T cell NHL – subcutaneous panniculitis

It is a rare subtype. They have an aggressive course and are characterized by the presence of lipomas or of white wax formations and the presence of hemophagocytic syndrome with fever, hepatosplenomegaly, pancytopenia and fatal complications. (16,26) It is associated with autoimmune diseases. Immunophenotypically: CD 3 + CD 4 + CD 8 -, or CD 3 +, CD 4 -, CD 8 +; rarely have a gamma/delta phenotype.(27)

Mycosis fungoides/Szary Syndrome-MF/SS

It is a rare disease, occurs in male adults over 50 years old, regardless of race, unspecified etiology. If MF / SS is a condition usually treated in dermatology clinics being for a long time confused with infectious paracheratosis, seborrheic or exfoliative dermatitis, neurodermitis, psoriasis or plaques parapsoriasis, SS syndrome(leukemic form of MF) is becoming a serious hematologic problem regarding treatment, evolution and prognosis. *Morphological* MF / SS lymphocytes have cerebriform nuclei. Immunophenotypically express mature helper T lymphocyte aspect CD2, CD3, CD4, CD5. Histopathologically skin lesions are characterized by infiltration of the superficial dermis and profound epidermis with atypical lymphocytes, where pseudoabscesses Pautrier can be observed,

CLINICAL ASPECTS

centrifugal expansion of the lymphoid infiltrate and associated infiltrating cellular polymorphism (lymphocytes, plasma cells and histiocytes). Sezary syndrome represents the triad: exfoliative erythroderma, poliadenopathy, leukemic download into circulation. Atypical cells in the blood varies between 15-20% in cases with plaques and cutaneous tumors and over 90% in forms with generalized erythroderma. Survival rate depends on the stage. Average survival is 8-9 years, death occurs usually by septic complications.(28,29,30)

Prolymphocytic T leukemia

It was described in 1987. Unlike the type-B has an aggressive behavior. It represents 30% of type T leukemia. *Clinical* occurs in elderly with hepatosplenomegaly, skin disease, anemia and thrombocytopenia, leukocytosis. Cell morphology of LPL is kidney-shaped nucleus, irregular, with small nucleoli, eosinophilic cytoplasm. They have a mature T cell phenotype CD4 +, CD8 -, and 10% have CD4 - CD8.

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CLINICAL ASPECTS

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