

World Health Organization Classification of tumors of hematopoietic and lymphoid tissues, 4th edition, 2008 – major changes from the 3rd edition, 2001

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ABSTRACT

The World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues (4th edition, 2008) represents an update of the 3rd edition, 2001. A summary of these changes in myeloproliferative disorders, myelodysplastic syndrome, acute myeloid leukemias, B and T precursor cell neoplasms, and mature B, T and NK cell neoplasms is presented below. Understanding the molecular genetic changes and the results achieved with innovative therapeutic approaches in these groups of diseases require continuous reassessment of its classification, justifying the major changes discussed here^{1,3-5}.

Keywords: World Health Organization; myelodysplastic syndromes; myeloproliferative disorders; lymphoproliferative disorders; classification.

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MYELOPROLIFERATIVE NEOPLASMS (MPN)

This group of neoplasms underwent considerable changes in this new edition. The term myeloproliferative diseases was replaced by myeloproliferative neoplasms (MPN), stressing its clonal character. The recognition of mutations/rearrangements in protein-coding genes with tyrosine kinase activity, such as *BCR-ABL* (chronic myeloid leukemia [CML]), *JAK2* (polycythemia vera [PV]), primary myelofibrosis [PMF], essential thrombocythemia [ET]), and *KIT* (mastocytosis), and of myeloid and lymphoid diseases concomitant with *PDGFRA*, *PDGFRB*, and *FGFR1* rearrangements was important to define new disease groups and change previous diagnostic criteria.

The major changes in MPN classification are summarized as follows:

1. Mastocytosis, previously studied in a separate chapter, has been included in this category, keeping the same classification⁶.

2. Some cases that previously met the criteria for chronic eosinophilic leukemia (CEL) migrated into the group of myeloid and lymphoid neoplasms with eosinophilia and abnormalities in *PDGFRA*, *PDGFRB* and *FGFR1* genes. In the absence of either these rearrangements or the *BCR-ABL* fusion, the disease belongs to the CEL category with no other specification.

3. The diagnostic algorithms for PV, ET and PMF were changed, including mutational status of *JAK2* gene and other correlate genes. Bone marrow histological findings, particularly for megakaryocytes, were strengthened as diagnostic criteria.

4. Criteria for accelerated phase CML were maintained and new ones were proposed. There is still controversy regarding its clinical relevance in the tyrosine kinase inhibitors era.

5. The platelet count threshold for ET was reduced from 600,000/mm³ to 450,000/mm³.

MYELOID AND LYMPHOID NEOPLASMS WITH EOSINOPHILIA AND ABNORMALITIES IN *PDGFRA*, *PDGFRB*, and *FGFR1* GENES

They constitute a new group in the 2008 WHO Classification. These rare neoplasms are defined as clonal diseases caused by abnormalities in genes coding for alpha or beta chains in receptors with tyrosine kinase activity: platelet-derived growth factor receptor (PDGFR) or fibroblast growth factor receptor (FGFR1). The relevance of recognizing these neoplasms is their response to tyrosine kinase inhibitors, particularly imatinib. Neoplasms with such genetic abnormalities are postulated to arise from a myeloid-lymphoid pluripotent progenitor cell. A frequent feature is eosinophilia, with these diseases being previously known as CEL, chronic myelomonocytic leukemia (CMML) with eosinophilia, myeloproliferative syndrome/

myelodysplastic syndrome (MPS/MDS) with eosinophilia, and hypereosinophilic syndrome. The clinical feature is heterogeneous, usually associated with MPN or even with lymphoid disease. Some cases may present as acute myeloid leukemia (AML), B or T cell acute lymphoid leukemia (ALL), T lymphoblastic lymphoma, and disorders with mast cell proliferation. The most frequent gene rearrangement changing *PDGFRA* is the *FIPL1-PDGFRB* fusion resulting from cryptic deletion of chromosome region 4q12, detected only by molecular techniques. On the other hand, rearrangements in *PDGFRB* (located at 5q33) genes and *FGFR1* (located at 8p11) gene can be detected by karyotyping or fluorescence *in situ* hybridization (FISH) with a disrupt probe identifying translocations involving partner genes.

MYELODISPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDN/MPN)

These diseases include clonal myeloid neoplasms that present clinical and laboratory features of both myelodysplasia and myeloproliferation. While some cases of atypical *BCR/ABL*-negative CMML and CML present with *JAK2* mutation, these diseases are better characterized by changes in intracellular signaling pathways *RAS/MAPK*. To be included in this group, the exclusion of *BCR-ABL* gene fusion and rearrangements in *PDGFRA*, *PDGFRB*, and *FGFR1* genes are required.

Other changes in this group of neoplasms include:

1. Atypical CML has been renamed *BCR/ABL*-negative atypical CML.

2. Refractory anemia with ring sideroblasts associated with thrombosis (RARS-T), also known as essential thrombocythemia with ring sideroblasts, was included in a provisional category. RARS-T diagnostic criteria include not further classifiable MPN/MDN criteria associated with RARS morphological criteria, platelet count over 450,000/mm³, and the presence of anomalous megakaryocytes observed in ET or PMF. About 60% of RARS-T has a *JAK* mutation or a *MPL* W515/L mutation.

MYELODYSPLASTIC SYNDROMES (MDS)

MDS are clonal disorder of hematopoietic precursor cell characterized by cytopenias, dysplasia in one or more myeloid lineages, ineffective hematopoiesis, increased apoptosis, and an AML-prone course. The diagnostic criterion of < 20% blasts in bone marrow (BM) and peripheral blood (PB) is maintained. The differential diagnosis between MDS and AML is strengthened when the presence of > 50% erythroid cells is observed in BM. The presence of > 20% blasts among non-erythroid cells, non-plasma cells, and non-lymphocytes defines AML, whereas < 20% blasts defines MDS. For the latter condition, the percentage number of blasts among all nucleate cells is again used

to classify MDS. Within this classification, the etiology of MDS with isolated del(5q) is better elucidated through the participation of the *RPS14* gene, involved in ribosome protein function.

The main changes in the new WHO classification include:

1. The creation of subtype refractory cytopenia (RC) with dysplasia in one strain, including refractory anemia, refractory neutropenia, and refractory thrombocytopenia, some of them previously included in the group of not further classifiable MDS (I/MDS). This group includes uni- or bicytopenias, < 5% blasts in BM, presence of dysplasia in only one lineage, and < 15% ring sideroblasts.

2. The refractory cytopenia with multiple lineage dysplasia (RC/MLD) also comprises RC/MLD with ring sideroblasts, since there is no difference in prognosis between them.

3. I/MDS diagnosis can be defined in the presence of three conditions: 1) presence of RC or R/MLD criteria, but with 1% of blasts in PB; 2) presence of RC with pancytopenias; and 3) presence of persistent cytopenias with < 1% of blasts in PB and < 5% in BM, dysplasia in < 10% of cells in one or more myeloid lineages and cytogenetic abnormalities associate with MDS.

4. Inclusion of pediatric MDS (P-MDS) and a provisional category, childhood refractory cytopenia (P-RC). For children with 2% to 19% blasts in PB and 5% to 19% blasts in BM, the same criterion as for RAEB is used, as in adults. As for RC-P, comprising about 50% of P-MDS cases, it is characterized by persistent cytopenias, < 5% blasts in BM and < 2% in PB, associated with dysplasias and marrow hypocellularity in 75% of cases. The differential diagnosis between hypoplastic P-RC and bone marrow aplasia is difficult and particularly based on aspirate dysplasias and BM histology.

ACUTE MYELOID LEUKEMIA (AML) AND RELATED-PRECURSOR NEOPLASM

In order to consider a leukemia diagnosis, blasts must correspond to more than 20% in the differential count of 200 cells in PB or 500 cells in BM. In the 2008 WHO classification, genetic changes were incorporated into AML diagnostic algorithms.

AML WITH RECURRENT GENETIC ABNORMALITIES:

Leukemias with recurrent genetic abnormalities coding for transcription factors and encompassing AML with t(8;21) or ETO/AML1 (currently termed RUNX1/RUNX1T1), t(15;17) or PML/RARA, inv(16) or CBFβ/MYH11 and 11q23 or MLL were given well-defined new elements described below. Discovering the importance of mutated genes (*KIT*, *FLT3*, *MLL*, *CEBP*, *NPM1*, *WT1*,

BAALC, *ERG*, and *MN1*) in leukemogenesis allowed AML subtype characterization of AML with normal karyotype, enabling their designation as specific entities. In this setting, the most important changes were as follows:

1. AMLs with recurrent genetic abnormalities, such as t(8;21) (q22;q22), inv(16)(p13.1q22) or t(16;16) (p13.1;q22) and promyelocytic leukemia (PML) with t(15;17)(q22;q12), are considered leukemia regardless the blast percentage in peripheral blood or bone marrow.

2. The so-called variant PMLs, i.e., with translocations involving other chromosomes, such as, 11q23(*ZBTB16*), 11q13(*NuMA*), 5q35(*NPM*) or 17q11.2(*STAT5B*) should be designated with the specific partner. Not all of them are responsive to ATRA or have a typical morphology.

3. ALM with 11q23 or MLL change was reviewed and ALM with t(9;11)(p22;q23) or MLLT3/MLL, which is the most frequent, will be so designated. The other changes involving 11q23 with over 80 partners are still termed MLL abnormalities. However, it is recommended that variant translocations should also be specified. Other abnormalities, such as partial tandem duplication, are not allocated in this category.

4. Three new cytogenetic entities were added since they presented different morphology and clinical behavior: a) AML with t(6;9)(p23;q34) or DEK/NUP214; b) AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) or RPN1/EV11; and c) megakaryoblastic ALM with t(1;22) (p13;a13) or RB<15/MKL1.

5. Two provisional categories were incorporated: AML with mutated *NPM1* and AML with mutated *CEBPA*. Even though *FLT3* mutation has not been included into a provisional category, this mutation assessment is recommended in all cases of normal karyotype AML.

AML WITH MYELODYSPLASIA-RELATED CHANGES

Regarding AML with multiple lineage dysplasia initially introduced in the classification to incorporate AML with dysplastic characteristics, unfavorable karyotype, increased expression of multiple drug resistance (MDR) glycoprotein, and poor response to chemotherapy, it is now termed AML with myelodysplasia-related changes. For this purpose, criteria have been expanded to include a history of previous myelodysplastic (MDS) or myelodysplastic/myeloproliferative (MDS/MPS) syndrome. Over 20% of blasts must be found in PB or BM, it must have progressed from MDS or MDS/MPS previously documented, show chromosome changes specifically related to MDS and exhibit dysplasia in 50% or more in two myeloid lineage cells. If karyotype is normal, *FLT3*, *NMP1*, and *CEPBA* mutations must be investigated; if present, they must be reported in the diagnosis.

THERAPY-RELATED MYELOID NEOPLASMS (T-MN)

Regarding therapy-related myeloid neoplasm, previously encompassing AML, MDS, and MDS/MPS, it now presents as a single AML subgroup. T-AML, T-MDS, and T-MDS/MPS must be considered, from the biologic point of view, as a single entity. There is no longer a recommendation to differentiate between them according to the therapeutic agent used, i.e., radiation therapy, alkylating agent or topoisomerase II inhibitor, as previously required. Despite the chromosome changes in cases of neoplasms secondary to therapy are practically identical to the myelodysplasia-related AML changes, the former have, as a rule, worse outcome than the latter with the same cytogenetic change. This fact suggests they are biologically dissimilar diseases.

AML NOT OTHERWISE SPECIFIED (AML, NOS)

AML, NOS, which includes all cases that did not meet criteria for the other categories, became empty as other subgroups have been recognized. A number of erythroid or megakaryoblastic leukemia cases can now be reclassified as AML with myelodysplasia-related changes. The option was to keep the leukemia name, according to the morphological, cytochemical, and immunophenotypic characteristics of the affected cell. For this subgroup, more than 20% blasts in PB or BM are required, except for acute erythroid leukemia, which is based on abnormal erythroblasts percentage for pure erythroid and on myeloblast percentage permeating non-erythroid cells for erythroid/myeloid type. The promonocytes in leukemia with monocytic differentiation are considered as blasts in the counting.

THREE NEW MYELOID ENTITIES HAVE BEEN CONSIDERED

1. Myeloid sarcoma, previously termed granulocytic sarcoma or chloroma, consists of extramedullary blasts proliferation from one or more myeloid lineages, replacing the original tissue normal architecture.

2. Myeloid proliferations related to Down syndrome comprise abnormal transient myelopoiesis and myeloid leukemia, showing peculiar morphology, immunophenotype, clinical, and molecular features with *GATA1* mutation.

3. Blastic plasmacytoid dendritic cell neoplasm, defined as derived from plasmacytoid dendritic cell precursors; it was previously recognized either as NK blastic cell lymphoma or CD4⁺/CD56⁺ hematodermic neoplasm. It is a neoplasm considered now among myeloid neoplasms, being clinically aggressive and characterized by skin damage associated with regional lymphadenopathy.

ACUTE LEUKEMIAS OF AMBIGUOUS LINEAGE

The new version of the WHO, 2008, allocates these diseases to a separate chapter and changes diagnostic criteria. Thus, cases with no specific lineage markers are termed undifferentiated acute leukemia, usually expressing CD34,

HLA-Dr and/or CD38 and sometimes TdT, but they do not express specific myeloid or lymphoid antigens. The leukemias whose blasts express concomitantly antigens from more than one lineage in the same cell or have distinct blast populations from different lineages are termed mixed phenotype acute leukemias.

A provisional entity was created, a lymphoblastic leukemia/lymphoma of NK cells. The majority of cases previously recognized as blastic NK cell lymphoma/leukemia are now termed blastic plasmacytoid dendritic cell neoplasm, as mentioned above. Although the neoplasm phenotype of true NK cell precursors is not clear, the diagnosis should be considered when blasts express CD56 with antigens associated with immature T cell, such as CD7 and CD2, in the absence of any B expression or myeloid antigen and with no rearrangement of T cell receptor gene.

LYMPHOID PRECURSOR NEOPLASMS: B LYMPHOBLASTIC LEUKEMIA/LYMPHOMA AND T LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

The designation B precursor leukemia/lymphoma was replaced by B lymphoblastic leukemia/lymphoma, with caution being exerted at incorporating genetic changes. Next, the convention used for therapeutic approach to distinguish lymphoma from leukemia, considering the presence of tumor mass accompanied by 25% or more nucleolate cells in bone marrow (lymphoblasts) is considered as acute lymphoblastic leukemia rather than lymphoma. On the other hand, as an ALL rarely shows low lymphoblast percentage, if there are < 20% blasts, ALL diagnosis should be postponed until irrefutable evidence confirms the diagnosis. Furthermore, in a rare circumstance when there are < 20% blasts in bone marrow, in the absence of chromosome change, but in the presence of recurrent chromosome change associated with ALL, the diagnosis of ALL could be considered, since the search for extramedullary mass has been exhaustive in order to rule out lymphoblastic lymphoma. Attention is drawn also to the detail that the designation of B-ALL must not be used for Burkitt's lymphoma, which is a neoplasm of mature B cell. Given the fact that several chromosome abnormalities define clinical, immunophenotypic, and prognostic features, they are now considered distinguished entities, e.g., ALL/lymphoma with t(1;19)(q23;p13.3), TCRF3/PBX1 etc. In this setting, ALL cases in children with normal karyotype should be complemented by investigating t(12;21)(p13;q22) by fluorescence *in situ* hybridization (FISH) or ETV6/RUNX1 rearrangement undetectable by classical cytogenetics, as this abnormality identifies a favorable prognosis. Similarly, all the patients should be assessed for *Philadelphia* chromosome presence and/or BCR/ABL1 rearrangement in view of their poor prognosis. Cases with eosinophilia should be additionally investigated for t(5;14)(q31;q32) or IL3/IGH, as they can

have low blast percentage, and this chromosome abnormality is enough to diagnose ALL. Moreover, when faced with eosinophilia, *FGFR1* rearrangements should also be sought, which, if present, describe the diagnosis of leukemia/lymphoblastic lymphoma associated with *FGFR1* rearrangement.

In the absence of any cytogenetic or molecular change after comprehensive analysis, ALL is classified as B lymphoblastic leukemia/lymphoma with no other specification. T lymphoblastic leukemia/lymphoma shows frequent chromosome rearrangements involving 14q11.2, 7q35, 7p14-15, *loci* of alpha, beta, and gamma T cell receptors, respectively. As the pathogenetic significance of such abnormalities is not clear yet, this leukemia subtype is not subclassified according to the genetic change.

MATURE B CELL NEOPLASMS

1. Chronic lymphoid leukemia (CLL)/lymphocytic lymphoma – the criteria for diagnosing CLL were reviewed according to the International Workshop on CLL⁷.

– The diagnosis of CLL, in the absence of extramedullary involvement, requires $> 5 \times 10^9$ B cells/L with CLL immunophenotype in PB. Patients with low level of lymphocytosis persisting for three months and accompanied by cytopenia or symptoms related to the disease also can be concluded as CLL.

– The term LL is used in cases with CLL tissue morphology and immunophenotype, enlarged lymph nodes without cytopenia due to infiltration by CLL and $< 5 \times 10^9$ B cells/L in PB.

– The category of monoclonal B lymphocytosis is recognized and defined as the presence of monoclonal B lymphocyte in PB with immunophenotype in most cases of CLL, but without CLL criteria. This entity clinical significance has not been defined yet.

2. Among splenic lymphomas, the not further classifiable B cell lymphoma/leukemia category has been introduced, including two rare provisional entities, the splenic diffuse red pulp small B-cell lymphoma and the hairy-cell leukemia variant, whose relationship between themselves and between them and the splenic lymphoma with villous lymphocytes still needs to be better defined. The term not further classifiable B-cell lymphoma/leukemia must be used for the small B-cell lymphomas showing neither the criteria for the above entities nor the criteria for any other classical small B-cell lymphoma.

– Splenic diffuse red pulp small B-cell lymphoma is considered synonymous with a less specific entity termed splenic lymphoma with villous lymphocytes, with some overlapping with hairy-cell leukemia variant.

– Hairy-cell leukemia variant only changes position in the classification, as it is no longer considered biologically related to hairy-cell leukemia.

3. Lymphoplasmacytic lymphoma (LPL) – diagnosis criteria have not been changed, but the diagnosis of small B-cell lymphomas with plasmacytic differentiation, followed by possible differential diagnosis in those circumstances when LPL criteria are not met or for the classical entities in the small B-cell lymphoma group showing plasmacytic differentiation is recommended. Regarding Waldenström macroglobulinemia (WM), according to the International Workshop on WM, 2002⁸, it is now defined as LPL with BM involvement and monoclonal gammopathy at any serum level.

4. The nodal marginal zone lymphoma loses “B-cell” and pediatric cases are separately classified, since they are usually localized, having an excellent prognosis.

5. Follicular lymphoma (FL) – regarding histological grading, the criteria remain the same, but grades 1 and 2 are now considered together as low level. Regarding grade 3, the criteria remain for 3A and 3B. Focal grade 3 areas in a low level FL should be reported and semi-quantified when the diagnosis is made. In a grade 3 FL (A or B), the presence of a diffuse component (may be confirmed by CFD absence through CD21 or CD23) deserves an additional separate diagnosis of diffuse large B-cell lymphoma (DLBCL), estimating its ratio. DLBCL areas are found in 60% to 80% of FL-3B, being less frequent in FL-3A. FL variants are recognized, including:

– Pediatric FL – characteristically BCL2-negative, t(11;14)BCL2/IGH-negative and often grade 3, but with a favorable course.

– Primary FL of the gastrointestinal tract – often in duodenum, similar to node FL, usually localized, with a good outcome even if untreated.

– *In situ* follicular neoplasm – CD10+/BCL2 center-cell populations in varying proportions inside some follicle germinal centers – their clinical significance is still unclear.

6. Primary cutaneous follicle center lymphoma – appears as a separate entity, included since the WHO-EORTC classification⁹.

7. Mantle cell lymphoma (MCL) – diagnostic criteria are still the same, but a broad clinical spectrum is assumed with more indolent cases, particularly with predominant BM and PB involvement. An *in situ* MCL form, with nuclear clinical and biological significance, has been described. At the other extreme of the clinical spectrum there are the aggressive variants termed blastoid (similar to the lymphoblastic lymphoma) and pleomorphic (similar to DLBCL). A cell proliferation assessment through mitosis count or Ki-67+ cell ratio is considered a prognosis factor relevant although having no definite cut-off.

8. Diffuse large B-cell lymphoma (DLBCL) – a long list of new DLBCL entities and subtypes particularly related to specific sites and the association with virus (EBV and/or HHV8) is introduced; these virus have frequent morphologic and immunophenotypic characteristics of terminal (plasmablastic) B-cell differentiation.

MATURE T- AND NK-CELL NEOPLASMS

The 2008 WHO classification for T/NK neoplasms brought information regarding diagnostic criteria, etiology, and prognosis in this large neoplasm group. In a didactic way, T/NK neoplasms will be presented in four groups: 1) Predominantly nodal T lymphomas; 2) Extranodal T/NK lymphomas; 3) Cutaneous T/NK lymphomas; and 4) Predominantly leukemic presentation T/NK lymphomas. For a summary on the major changes in T-cell neoplasms (Table 1).

1. Predominantly nodal presentation T lymphomas

The largest group of T lymphomas, the so-called peripheral T-cell lymphomas not otherwise specified underwent few changes. The most subtle regards a change from unspecified to not otherwise specified. The variants T zone lymphoma and the lymphoepithelioid lymphoma (Lennert's lymphoma) were maintained, with the follicular variant being incorporated. This latter variant can simulate the nodular pattern B-cell lymphomas (FL, MZL, and MCL) and would originate in T-cell follicular helper (TFH), as would the angioimmunoblastic T-cell lymphomas (AITL) (see below).

The anaplastic large cell lymphomas (ALCL) have been subdivided into ALK-positive and ALK-negative. This makes this protein expression assessment mandatory. The ALCL/ALK-negative lymphomas have worse prognosis than the ALCL/ALK-positive lymphomas, though their outcome is still superior to that of peripheral T-cell lymphomas NOS. The ALCL/ALK-negative lymphomas diagnosis implies the presence of classical morphology, cytotoxic cells, less frequent EMA expression, and more frequent T markers expression. In ALCL/ALK-positive lymphomas, the criteria remained the same, with a new variant addition (Hodgkin-like, similar to nodular sclerosis) to recognized variants (small cell and e lympho-histiocytic).

Finally, the ALCL was maintained with the same nomenclature and diagnostic criteria, being recorded the recognition of its origin cell as a specific CD4+ cell population designated TFH (T-cell follicular helper). Typical markers of these cells, such as cytokine CXCL13, PD1 protein (program death 1), and CD10 can be used in these lymphomas identification.

2. T/NK-cell neoplasms predominantly extranodal

Few changes were introduced in this group of lymphomas, with the same four entities being maintained: enteropathy-associated T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, hepatosplenic T-cell lymphoma, and extranodal T/NK-cell lymphoma, nasal type. The latter two (hepatosplenic and nasal types) were maintained practically unchanged.

The subcutaneous panniculitis-like T-cell lymphoma, in the 2008 WHO classification, has not included those with gd T cells origin, which will be included with cutaneous lymphomas (see below). What is new in this classification for these lymphomas is the recognition that these neoplasms are associated with autoimmune disorders (specially lupus erythematosus) and share similarities with deep lupus panniculitis. The cells are CD8+ expressing granzyme B, perforin and bF1. In contrast, the cutaneous gd T-cell lymphoma does not express CD56; hemophagocytosis is observed in less than 20% of cases and is accompanied by a better prognosis.

The enteropathy-associated T-cell lymphomas were subdivided in type I (classical) and type II (monomorphic), both with poor prognosis. The classical type corresponds to the great majority of cases and is usually associated with celiac disease, with varying histological and clinical presentation. Most cells are large, there is an accompanying inflammatory infiltrate and the cells present CD3+/CD5-/CD7+//CD4-CD8-20%+/CD103+/granzyme/perforin+CD30± immunophenotype. The type II or monomorphic type represents less than 20% of total cases; it has a more uniform histopathological presentation and shows a different immunophenotypic profile CD8+/CD56+. The enteropathy-associated T-cell lymphoma is still recognized in its *in situ* form, characterized by clonal intraepithelial lymphocytes, manifesting clinically as either a celiac disease refractory to gluten withdrawal or an ulcerative jejunitis.

The definitions of mycosis fungoides and Sézary syndrome were not changed. The lymph node classification was better characterized, defining more precisely the categories N1 (dermatopathic lymphadenopathy with atypical cell clusters – between three and six cells), N2 (dermatopathic lymphadenopathy with scarce cerebriform cells < 7.5 mm and architecture maintained) and N3 (evident neoplastic involvement, even if it is partial). The clinical staging was also changed, and new pathogenetic factors were defined.

3. T/NK-cell lymphomas with cutaneous presentation

The cutaneous T/NK-cell lymphomas are classified as mycosis fungoides, Sézary syndrome, CD30-positive T-cell lymphoproliferative disorders, cutaneous gd T-cell lymphoma, and two provisional entities, CD8+aggressive epidermotropic cytotoxic T-cell lymphoma and cutaneous CD4+small/medium T-cell lymphoma.

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The CD30+ T-cell lymphoproliferative disorders include cutaneous primary ALCL, lymphomatoid papulosis, and borderline cases. Significant changes in diagnostic criteria for these entities were not observed, with three histological subtypes being recognized (A, B, and C) for lymphomatoid papulosis.

Table 1 – Major changes introduced into the T/NK-cell neoplasm group in the 2008 WHO classification

2001 WHO	2008 WHO	Comments
Angioimmunoblastic Lymphoma	Angioimmunoblastic Lymphoma	Definition of origin cell
Anaplastic Large Cell Lymphoma	2 variants based on ALK (+/-) expression	Prognostic importance
Unspecified Peripheral T-cell Lymphoma	Peripheral T-cell Lymphomas not Otherwise Specified	3 variants: lymphoepitelioid lymphoma, T zone lymphoma (2001 WHO) and follicular lymphoma (2008 WHO)
T/NK-cell lymphoma, nasal type	T/NK-cell lymphoma, nasal type	No changes
Enteropathy-associated T-cell lymphoma	Enteropathy-associated T-cell lymphomas	Two variants: classical and monomorphic types with genetic changes common to both
Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	No changes
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Only ab and associated with autoimmune disorder
Mycosis fungoides	Mycosis fungoides	New staging and new information about pathogenesis
Sézary syndrome	Sézary syndrome	New markers
Primary cutaneous anaplastic large cell lymphoma	Primary cutaneous anaplastic large cell lymphoma	Recognition of CD8+ cases
Lymphomatoid papulosis	Lymphomatoid papulosis	Three histological types
	Primary cutaneous gamma-delta T-cell lymphoma	Three histopathologic patterns: epidermotropic, dermic, and subcutaneous subtypes
	Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma	Provisional entity
	Primary cutaneous CD4+ small/medium T-cell lymphoma	Provisional entity
Blastic NK-cell lymphoma	Plasmacytoid dendritic cell neoplasm	Now it is one of the myeloid neoplasms
T-cell prolymphocytic leukemia	T-cell prolymphocytic leukemia	No changes
T-cell large granular lymphocytic leukemia	T-cell large granular lymphocytic leukemia	New etiological features and new markers
	Chronic lymphoproliferative disorder of NK-cells	Provisional entity
Aggressive NK-cell leukemia	Aggressive NK-cell leukemia	No changes
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Definition of the regulatory T-cell normal counterpart

The cutaneous gd T-cell lymphoma has already been noted and it was separated from panniculitis-like lymphomas. Much more often, these lymphomas affect the subcutaneous cellular tissue, but they do not spare the dermis and the epidermis, with epidermotropic, dermic and predominantly subcutaneous subtypes being recognized. Necrosis, angioinvasion and hemophagocytosis are often observed.

Two rare provisional entities were included. The first one is the cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, characterized by an aggressive course with necrosis and skin ulceration. The second entity is the cutaneous CD4+ small/medium T-cell lymphoma, with excellent prognosis. The differential diagnosis between these entities and reaction processes is difficult,

since they are associated with a plasma cell and B-lymphocyte infiltrate. The main diagnostic criteria are T antigen loss and clonal TCR clonal rearrangement. They are both entities whose molecular defects are unknown.

Finally, the blastic NK-cell lymphoma is excluded from this group and will be recognized as plasmacytoid dendritic cell neoplasm, as previously mentioned.

4. T/NK-cell neoplasms with predominantly leukemic presentation

The only significant change was the inclusion of chronic lymphoproliferative disorder of NK-cells as a provisional entity, characterized by chronic and indolent increase in NK-cell count, with difficult differential diagnosis using rational processes.

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