Background and Objectives. The REAL/WHO classification constitutes a new tool for the better understanding and treatment of malignant lymphomas. The authors focus on the key features of aggressive B- and T-cell lymphomas, aiming to contribute to the cross-talk between pathologists and clinicians.

Data sources and methods. Each lymphoma entity is analyzed on the basis of the most representative contributions in the literature and the authors' experience gained in studying more than 20,000 lymphoid tumors over a 20-year period.

Results. Guidelines for diagnosis and areas of interest for future clinico-pathologic studies are identified and discussed. Within this context, selected data obtained by the application of novel markers are presented.

Interpretation and Conclusions. The present knowledge and organization of malignant lymphomas now make the development of tailored therapies a feasible goal.

Key words: aggressive lymphoma, morphology, phenotype, genotype, behavior

In the clinical setting, the term aggressive lymphoma has recently substituted high grade malignant lymphoma, previously quoted in both the Working Formulation (WF) and Updated Kiel Classification (UKC). It is currently applied to lymphoid tumors characterized by survival measurable in weeks or months if not treated. This term was not adopted by the Revised European-American Lymphoma (REAL) classification for the reasons already reported in Part I (see Clinical categorization of malignant lymphomas paragraph). Aggressive lymphomas may show nodal, extranodal, systemic, or leukemic presentation, more often associated with rapidly growing masses and systemic symptoms. The main histologic varieties of aggressive lymphoma are listed in Table 1: they include neoplasms which are derived either from precursors or peripheral elements and can indifferently consist of small or large cells.

B- and T-cell precursor (lymphoblastic) lymphoma/leukemia

There is no chance of distinguishing between B- and T-cell lymphoblastic lymphomas/leukemias (LbL/Ls) by morphologic criteria alone. In fact, they both consist of small-medium sized elements, which display a high nuclear/cytoplasmic ratio, frequent irregular nuclear profile, condensed chromatin, and inconspicuous nucleoli (Figures 1a and 1b). The tumoral growth is characterized by frequent mitotic figures and apoptotic bodies, which attract numerous macrophages (Figures 1a and 1b). The distinction between the two forms does, however, become feasible on phenotypic grounds: this distinction is of paramount importance, since B- and T-cell tumors require different therapeutic approaches. In particular, immunohistochemistry, which can now be easily performed in routine sections thanks to the availability of new antigen retrieval techniques, allows the subclassification of LbL/Ls into subtypes (pro-B, pre-B, B-mature, pre-T, from cortical thymocytes, and from medullary thymocytes) according to a combination of key-markers (i.e. CD34, TdT, BSAP, CD79a, CD20, CD10, CIg, SIg, CD1a, CD2, CD3, CD4, CD5, and CD8) (Figures 1c-f). The detection of cytogenetic and/or molecular aberrations is prognostically relevant. Among tumors derived from B-cell precursors, t(12;21) with the formation of the TEL-AML1 fusion gene, t(3;21) and a hyperdiploid pattern between 51 and 65 represent favorable indicators; t(9;22), t(14;19), and a hypodiploid pat-
Table 1. Aggressive lymphomas.

<table>
<thead>
<tr>
<th>B-cell neoplasms</th>
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<tr>
<td>Precursor B-cell neoplasms</td>
</tr>
<tr>
<td>• Precursor B-lymphoblastic leukemia/lymphoma</td>
</tr>
<tr>
<td>Peripheral B-cell neoplasms</td>
</tr>
<tr>
<td>• Mantle cell lymphoma</td>
</tr>
<tr>
<td>• Follicular lymphoma grade III</td>
</tr>
<tr>
<td>• Diffuse large B-cell lymphoma</td>
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<tr>
<td>• Burkitt’s lymphoma/ Burkitt cell leukemia</td>
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<table>
<thead>
<tr>
<th>T-cell and putative NK-cell neoplasms</th>
</tr>
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<tbody>
<tr>
<td>Precursor T-cell neoplasms</td>
</tr>
<tr>
<td>• Precursor T-lymphoblastic lymphoma/leukemia</td>
</tr>
<tr>
<td>Peripheral T- and NK-cell neoplasms</td>
</tr>
<tr>
<td>• T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>• Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>Adult T-cell lymphoma/leukemia (HTLV-1+)</td>
</tr>
<tr>
<td>Extramedullary NK T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Peripheral T-cell lymphomas not otherwise specified (NOS)</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, primary, systemic</td>
</tr>
</tbody>
</table>

UKC,2,3 that termed it small-cleaved cell lymphoma and centrocytic lymphoma, respectively. At the state of the art, mantle cell lymphoma (MCL) belongs to the body of aggressive lymphomas, since its median survival is below 3 years.4,20,21 It involves the bone marrow in 70% of cases (Figure 2a) (with characteristic paratrabecular diffusion), the intestine in 30% of cases (where it can also present primarily), and the peripheral blood in 20-25% of cases (producing a leukemic picture).4,28 Conventional regimens are not effective in the treatment of MCL: recent data on a limited number of cases suggest a good response to high dose therapies followed by autologous bone marrow transplantation.21 At conventional light microscopy,4,20 the tumor can show a mantle zone, nodular or diffuse growth pattern (Figure 2b). In the first two instances, the differential diagnosis with a marginal zone (MZL) or a follicular center lymphoma (FCL) can be difficult. Tumors with a diffuse growth pattern are more easily recognized, although the distinction from B-cell chronic lymphocytic leukemia (B-CLL), lymphoplasmacytic lymphoma (LPL), MZL, and FCL may at times be problematic. The commonest form of MCL consists of small-medium sized elements, showing a narrow rim of slightly basophilic cytoplasm and indented nuclei, with moderately dispersed chromatin and a small central nucleus (Figure 2c). In this context, perivascular deposits of hyaline material and acidophilic histiocytes are often encountered. More rarely, MCL is characterized by the occurrence of small round cells, blastoid elements or a polymorphous population, which can lead to a misdiagnosis of B-CLL, Lbl/L or diffuse large B-cell lymphoma (DLBCL), respectively (Figure 2d).

Immunohistochemistry is of paramount importance for the identification of MCL: in fact – besides the positivities for CD19, CD20, CD22, and CD79a – it shows expression of CD5 and cyclin D14,20 (Figures 2e and 2f). The latter indicates bcl-1 gene rearrangement, which is due to the occurrence of t(11;14) in 70% of cases.5,20 It should be underlined that bcl-1 gene rearrangement is characteristic, but not pathognomonic of MCL, since it can occasionally occur also in other lymphoid tumors.23 In all instances, there is occasional positivity for IRF4 and regular expression of BSAP (23) and bcl-2 gene product (Figures 2g and 2h): although the latter does not depend on the presence of t(14;18), nevertheless it produces protection of neoplastic cells from apoptosis.4,20 The search for CD10, CD23, CD68, CD72, and bcl-6 product produces constantly negative results.4,20,28,29 The above mentioned phenotypic profile allows easy distinction of MCL from B-CLL (CD5+, CD23+, IRF4+),
of lymphoid cells and histiocytes among neoplastic elements. This might lead to overestimation of the frequency of grade III follicular lymphoma and overtreatment of a percentage of patients. Mitotic figures are numerous. Besides positivity for B-cell markers (BSAP, CD19, CD20, CD22, CD79a), immunohistochemistry displays expression of CD10 and bcl-6 molecules (Figure 3b) (Table 2). The antibodies anti-CD21, CD23, and CD35 show a loose meshwork of follicular dendritic cells, which originate from vessels with hyaline wall or represent remnants of pre-existing germinal centers, which are in turn CD10+, bcl-6+, and bcl-2- (Figure 2h). The Ki-67 marking varies from case to case: a multivariate analysis on 304 cases has recently shown that patients with higher proliferative indices have a more aggressive clinical course.26

Follicular lymphoma, grade III

This tumor, which shows either a follicular or follicular and diffuse growth pattern, contains more than 15 centroblasts/high power field (Figure 3a). The blast count should be performed by a experienced pathologist, because of the risk of including follicular dendritic cells and histiocytes among neoplastic elements. This might lead to overestimation of the frequency of grade III follicular lymphoma and overtreatment of a percentage of patients. Mitotic figures are numerous. Besides positivity for B-cell markers (BSAP, CD19, CD20, CD22, CD79a), immunohistochemistry displays expression of CD10 and bcl-6 molecules (Figure 3b) (Table 2). The search for the bcl-2 gene product can at times provide negative results.29,30 The latter finding might lead to overestimation of the frequency of grade III follicular lymphoma and over-treatment of a percentage of patients. Mitotic figures are numerous. Besides positivity for B-cell markers (BSAP, CD19, CD20, CD22, CD79a), immunohistochemistry displays expression of CD10 and bcl-6 molecules (Figure 3b) (Table 2). The antibodies anti-CD21, CD23, and CD35 show a loose meshwork of follicular dendritic cells, which originate from vessels with hyaline wall or represent remnants of pre-existing germinal centers, which are in turn CD10+, bcl-6+, and bcl-2- (Figure 2h). The Ki-67 marking varies from case to case: a multivariate analysis on 304 cases has recently shown that patients with higher proliferative indices have a more aggressive clinical course.26

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This tumor, which shows either a follicular or follicular and diffuse growth pattern, contains more than 15 centroblasts/high power field (Figure 3a). The blast count should be performed by a experienced pathologist, because
Table 2. Phenotypic profile of 110 aggressive B-cell lymphomas.

<table>
<thead>
<tr>
<th>CD3+</th>
<th>CD20+</th>
<th>CD79a+</th>
<th>CD10+</th>
<th>Bcl-2+</th>
<th>Bcl-6+</th>
<th>CD30+</th>
<th>CD138+</th>
<th>IRF4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCL/III</td>
<td>0/12</td>
<td>12/12</td>
<td>12/12</td>
<td>13/12</td>
<td>11/12</td>
<td>12/12</td>
<td>2/12</td>
<td>0/12</td>
</tr>
<tr>
<td>DLBC/NOS</td>
<td>0/35</td>
<td>35/35</td>
<td>35/35</td>
<td>35/35</td>
<td>35/35</td>
<td>35/35</td>
<td>35/35</td>
<td>0/10</td>
</tr>
<tr>
<td>DLBC/CB</td>
<td>0/5</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>5/5</td>
<td>0/5</td>
</tr>
<tr>
<td>DLBC/IB</td>
<td>0/10</td>
<td>10/10</td>
<td>10/10</td>
<td>10/10</td>
<td>10/10</td>
<td>10/10</td>
<td>10/10</td>
<td>10/10</td>
</tr>
<tr>
<td>DLBC/AAN</td>
<td>0/2</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
<td>2/2</td>
</tr>
<tr>
<td>PMLBC</td>
<td>0/24</td>
<td>24/24</td>
<td>24/24</td>
<td>24/24</td>
<td>24/24</td>
<td>24/24</td>
<td>24/24</td>
<td>24/24</td>
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<tr>
<td>BT</td>
<td>0/15</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
<td>15/15</td>
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</tr>
<tr>
<td>BA</td>
<td>0/7</td>
<td>7/7</td>
<td>7/7</td>
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<td>7/7</td>
<td>7/7</td>
<td>7/7</td>
<td>0/7</td>
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</table>


Diffuse large B-cell lymphoma

The tumor may develop de novo or derive from a previous indolent lymphoma, such as B-CLL, LPL, MZL, or FCL.4

On morphologic grounds,4 DLBCL consists of large cells (mean diameter = 20 µm), more often characterized by pronounced nuclear pleomorphism, prominent nucleoli, and a rim of basophilic cytoplasm (Figure 4a). The neoplasm grows diffusely, at times spreading through residual sinuses. Mitotic figures are always numerous. Some macrophages phagocytizing nuclear debris can be encountered. In a minority of cases one cytotype predominates over the others, thus allowing the subclassification of the process into the following forms: centroblastic, immunoblastic, anaplastic, or with large multilobated nuclei (Figures 4b-d). A further morphologic variant of the tumor, characterized by a high content of reactive T-lymphocytes, is termed T-cell-rich B-cell lymphoma (Figure 4e) and can be confused with lymphocyte-predominant Hodgkin’s disease.4 35-37 This variant occasionally shows prominent angiocentricity, thus producing the picture originally described as lymphomatoid granulomatosis.38 There is no consensus on the usefulness of distinguishing histologic subtypes of DLBCL: some groups have reported a more aggressive clinical course in patients with immunoblastic tumor.39,40

DLBCLs are also distinguished into different subtypes according to disease presentation: primary mediastinal or thymic,41-44 intravascular,45,46 body cavity-based,47,48 and pyothorax-associated.49 The primary mediastinal form more often occurs in females in the fourth decade of life and presents in stage I or II with bulky tumor and superior vena cava syndrome (Figure 4f). This variety seems to be very sensitive to third generation chemotherapy regimens, such as the MACOP-B; at relapse, it characteristically involves the liver, CNS, kidney, intestine, and gonads. The intravascular variant usually occurs at extranodal sites, such as the skin, lung or brain. The so-called body cavity-based or primary effusion lymphoma does not stem from contiguous neoplastic masses, is observed in immunodeficient patients (mainly HIV+), is associated with HHV8 infection, and displays a peculiar phenotypic profile (with regular expression of CD45, HLA-DR, EM A, CD30, CD38, and CD77, and lack of B- and T-cell markers). The derivation of this tumor from peripheral B-cells is supported by the observed clonal rearrangements of Ig encoding genes.47 Finally, pyothorax-associated DLBCL develops in patients with a previous history of tubercular empyema, infiltrates the chest wall extensively, and shows regular EBV integration in the genome of neoplastic elements (Figure 4g).

On phenotypic grounds (Table 2), at least three main groups of DLBCL can be distinguished: CD10+/bcl-6+, CD10+/bcl-6–, and CD10–/bcl-6–.50,51 The first group corresponds to neoplasms which derive from germinal center cells – either de novo or following transformation of a pre-existing FCL – and are characterized by strong-moderate expression of CD20, CD79a, and CD138, and show CD20, CD79a, and CD138 expression. The remaining two categories appear to be more heterogeneous. In fact, they include tumors with the following phenotypic profiles: a) bcl-6+/bcl-2+/CD10– (possibly also derived from germinal center cells), b) bcl-6+/bcl-2+/CD10+, and c) bcl-6+/bcl-2+/CD10+/CD20–/CD30+, CD79a+/CD138+, and CD10+/CD30–/CD79a+/CD138–/CD20+, CD10–/CD30+ (with anaplastic morphology) (Figure 4k-o). Interestingly, the leukocyte common antigen/CD45 is absent in about 30% of DLBCLs of the immunoblastic and anaplastic types.43,52 The expression of the bcl-2 gene product deserves special attention: in three
Burkitt’s lymphoma

Burkitt gave the prototypic description of this tumor in 1955, based on series of cases observed in Central Africa. The neoplasm appears monomorphic and consists of medium-sized elements, with deeply basophilic, vacuolated cytoplasm and round-oval nuclei, showing reticulated chromatin and 2-6 small nucleoli (Figure 5a). The process is characterized by a cohesive growth pattern, extremely numerous mitotic figures, abundant apoptotic bodies, and frequent macrophages, which produce a starry-sky appearance (Figure 5a).

At present, two types of Burkitt’s lymphoma (endemic and sporadic), as well as a Burkitt’s-like tumor, are distinguished. Endemic Burkitt’s lymphoma is characteristically observed in the malarial areas of Central Africa, where it affects children and young adolescents, involving the mandible or gonads and showing regular EBV integration in the genome of neoplastic cells. Its response to therapy is quite good. The sporadic form, which is definitely isomorphic, occurs in Western countries among young people and adults, the latter often being sero-positive. The tumor can present in the intestine, rectum, gonads or CNS, is highly aggressive and requires the administration of protocols normally applied to patients with acute Lb leukemias. Only 25% of HIV-negative individu-
that these translocations can also occur in lymphomas which have completely different morphology, histogenesis and natural history.55,57

T/ NK-cell lymphomas

Peripheral T/NK-cell lymphomas (PTCLs) represent about 10% of all lymphoid tumors in Western countries.4,63-65 For practical purposes, they should be divided into anaplastic and non-anaplastic forms. The latter are rare clinico-pathologic entities, which are characterized by marked cellular pleomorphism and occur at extranodal sites in at least 1/3 of cases (Figures 6a and 6b). Extranodal non-anaplastic PTCLs usually carry cytotoxic phenotype (TIA-1+) with frequent co-expression of activation markers (granzyme-B+, perforin+), and tend to develop in patients with an immunodeficient status, often following an organ transplantation.65-78 Non-anaplastic PTCLs generally show defective T-cell antigen expression (CD2-CD8), display clonal rearrangements of the genes encoding for the T-cell receptor, and may be pathogenically related to a viral infection (such as HTLV1 for the adult T-cell lymphoma/leukemia occurring in Japan and EBV for the nasal T-cell lymphoma of Asian countries or AILD-type peripheral T-cell lymphoma) (Figure 6c).4,64,65 On the whole, non-anaplastic PTCLs have a very poor clinical course in spite of the aggressive therapies employed (complete remission rate: 50% overall survival at 5 years: 30-35%; disease-free survival at 5 years: about 20%).63-65,79 These frustrating results might be partially due to the little attention paid to non-anaplastic PTCLs in Western countries, which has not favored the development of ad hoc therapies.

The anaplastic form of PTCL, usually termed anaplastic large cell lymphoma (ALCL), has been more extensively studied because of its relatively high frequency in Western countries and more favorable response to therapy (overall survival at 5 years: about 80%) 19,63,80-85

ALCL was first described by Stein et al. in 1985 as a tumor characterized by large cells with a wide rim of cytoplasm (greyish-violet at Giemsa staining), variably shaped nuclei, prominent nucleoli, cohesive growth pattern, intrasinusaloid diffusion, and regular expression of the CD30 molecule (86) (Figures 7a and 7b). In 1988 it was included in the UKC among both B- and T-cell lymphomas.21 Subsequent studies on larger series of cases led to the identification of clinico-pathologic variants: a) primary systemic (of the common, giant-cell rich, lympho-histiocytic, small cell, Hodgkin’s-related/like, sarco-matoid, and signet ring cell types) (Figures 7c-j), b) primary cutaneous, and c) secondary.85-94 In 1994, the REAL classification restricted the term ALCL to neoplasms with T- or null-phenotype and regarded the Hodgkin’s-like (HL) variant as a provisional entity.4,82,83,87 These concepts have been maintained in the recently developed WHO scheme19 with two major differences: a) cutaneous ALCLs have been included among primary CD30+ lymphoproliferative disorders of the skin,68 and b) ALCL-HL has not been autonomously quoted because of the need for further studies. At the state of the art, primary nodal ALCL is regarded as a tumor with a very aggressive presentation, but also one which is very sensitive to chemotherapy.13,63,80-85

Over the last two years, the definition of ALCL has been further refined as the result of new findings, such as the expression of cytotoxic molecules and ALK protein.

About 80% of ALCLs display an activated cytotoxic phenotype (TIA-1+, granzyme B+, perforin+), irrespectively of clinical and histologic features.95-97 This feature represents an exception among nodal PTCLs, since the non-anaplastic forms reveal such a phenotype in no more than 20% of cases.69 For the time being, the expression of cytotoxic markers has more histogenetic relevance, and does not seem to affect the clinical course of the disease.

The expression of ALK protein is more often due to the occurrence of the (2;5)(p23;q35) translocation, which was described about 10 years ago as being characteristically associated with ALCL.98 Subsequent molecular studies have shown that (t;2;5) produces the formation of a hybrid gene, termed NPM/ALK, which encodes for a chimeric protein formed by the N-terminal region of nucleophosmin (numatrin/B23) and the entire cytoplasmic domain of the tyrosine kinase receptor ALK.99-103 The development of specific antibodies against intracytoplasmic ALK domain and the N- and C-terminal regions of NPM, as well as their systemic application to large series of cases,106-111 has revealed that:

1. About 60% of ALCLs do express the ALK protein,85,106,108,109,111
2. These cases correspond strictly to systemic forms, since cutaneous ALCLs are regularly negative:85,112 in particular, ALK-positivity is observed in the vast majority of the tumors with common morphology and in most if not all lympho-histiocytic and small cell variants, while it is much rarer in the Hodgkin’s-like and giant cell-rich forms (15-30%)85,109-111 (Figures 7h, i and k);
3. The ALK staining usually occurs both in the nucleus and cytoplasm of the neoplastic ele-
ments, since the hybrid NPM/ALK protein forms a heterodimer with normal NPM, which is a shuttle-protein involved in the transcription mechanism;\textsuperscript{85,103,109,111}  
4. the same nuclear and cytoplasmic staining pattern is also observed with the antibodies raised against the N-terminal region of NPM, but not with the ones specific for its C-terminal portion, which produce a nuclear positivity, since they react with normal NPM that is physiologically harvested within the nucleus;\textsuperscript{85}  
5. all ALK+ ALCLs carry t(2;5)(p23;q35);\textsuperscript{85}  
6. in a small number of ALCLs, ALK-positivity is limited to the cytoplasm (Figure 7f): this finding corresponds to the occurrence of chromosomal aberrations other than t(2;5), involving chromosome 2 at p23, such as inv(2)(p23;q35), t(1;2)(q21-25;p23), t(2;2)(p23;q23), or t(2;3)(p23;q21);\textsuperscript{113-118}  
7. ALK+ ALCLs invariably carry a T- or null-phenotype and result EMA\textsuperscript{+} and CD15\textsuperscript{-};\textsuperscript{4,19,85,109,111}  
8. besides the classic large cells, recently termed hallmark cells, these tumors show a small-cell component, which is particularly evident in the lympho-histiocytic and small-cell variants and can vary during the course of the disease (for instance, at the time of presentation and relapse);\textsuperscript{85,109,111}  
9. ALK+ ALCL is characterized by a spectrum of morphologic features which can reflect the ratio between large and small elements, the occurrence of fibrosis (which can be responsible for the HL appearance), and the presence of histiocytes or other reactive components, likely attracted by cytokines released by neoplastic cells;\textsuperscript{85,109,111}  
10. ALK positivity is never observed in B- and T-cell tumors other than ALCL, with the exception of a very rare plasmablastic tumor which shows cytoplasmic staining, but does not carry t(2;5) or variants;\textsuperscript{119}  
11. a search for the ALK protein in Hodgkin’s lymphoma is invariably negative;\textsuperscript{85,109,111}  
12. ALK protein is not detected in normal lymphocytes, thus representing an important indicator both for diagnosis and detection of minimal residual disease;\textsuperscript{85,107}  
13. ALK+ ALCLs more often affect patients under 30 years old and show a better response to therapy and more favorable clinical course than the ALK- ones.\textsuperscript{84,110}  

On the whole, the above mentioned findings strengthen the appropriateness of: a) restricting the term ALCL to tumors with T- or null-phenotype, b) keeping the cutaneous forms separate, and c) excluding any relationship between ALCL and Hodgkin’s disease. Furthermore, they provide more precise and practical criteria to be applied to the so-called ALCL-HL, as stated in the last version of the WHO Blue Book:\textsuperscript{19}  
a) ALK+ ALCL can occasionally show nodular aggregation and fibrosis, as seen in nodular sclerosing (NS)-HD;  
b) NS-HD may be rich enough in neoplastic cells to be confused with ALCL;  
c) in problematic cases, the expression of CD15, possibly in conjunction with positivity for B-cell markers, and the lack of TCR gene rearrangements and ALK protein favor the diagnosis of HD, while the negativity for CD15, the expression of T-cell markers and/or ALK protein, and the presence of TCR gene clonal rearrangements or NPM/ALK hybrid gene support the diagnosis of ALCL; cases which cannot be resolved by the combination of cell morphology, phenotype, and molecular data should be regarded as unclassifiable and submitted to a second biopsy or a treatment equally effective for ALCL and HD.\textsuperscript{120}  

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SAP was responsible for the conception and design of this review. SA and ES were responsible for drafting the article. GFO was responsible for the analysis and interpretation of morphologic data. SP and MP were responsible for analysis and interpretation of phenotypic data. PPP was responsible for analysis and interpretation of clinical data. BG was responsible for the analysis and interpretation of molecular data. PLZ and LL were responsible for revising the article critically. BF approved the final version of the paper.  
The criteria for the order of names were involvement in design and organization of the paper, laboratory research, analysis of clinical data and reviewing the paper. The order of the names was decided on the basis of each individual contribution to the above criteria.  
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