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CONTROVERSIES ON HODGKIN'S DISEASE AND ANAPLASTIC LARGE CELL LYMPHOMA

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ABSTRACT

Just one year ago the Italian Society of Pathology (S.I.A.P.) created a Study Group which included members of the most active Italian hematopathology teams. Prof. Pasquale Calapso was asked to chair the Group and Prof. Stefano Pileri to take care of secretarial duties. The aim of the Group is to spread hematopathologic knowledge among young pathologists and to promote activities that can contribute to updating Italian pathologists on topics of both speculative and diagnostic interest.

The first Workshop of the S.I.A.P. Hematopathology Group was held at the Palazzo dei Congressi in Bologna, November 20, 1993. About 150 pathologists from all over Italy took part in the meeting, which consisted of two sections devoted to: a) discussion of the boundaries between Hodgkin's disease and non-Hodgkin's lymphomas, and b) a case seminar illustrating the impact of immunohistochemistry in the diagnosis of bone-marrow biopsy. The first section included 5 presentations and a Round Table chaired by Prof. Luciano Fiore-Donati.

Below, the contributors to this section summarize the content of their presentations, which were aimed at answering specific questions the Organizers had put to them.

IS NODULAR PARAGRANULOMA A DISTINCT ENTITY?

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Current criteria for the diagnosis and subclassification of Hodgkin's disease (HD), as well as for its differentiation from non Hodgkin's lymphomas (NHL) are based on the peculiar morphological, immunological and clinical features of the process. In NHL, involved tissues show a relatively homogeneous population of neoplastic cells, while HD is characterized by a predominant reactive infiltrate in which the neoplastic components [Reed-Sternberg (RS) cells and their variants] represent only a small minority. In addition, most NHL correspond to a recognizable stage of either B or T cell differentiation, permitting them to be classified according to the normal counterpart in the lymphoid system. By contrast, the malignant lineage in HD still awaits definition and no specific markers have yet been provided for this task. All these considerations have led to the assumption that HD and NHL are unrelated diseases well characterized by distinctive histological and clinical pictures. In spite of this general consensus, some lymphoreticular neoplasms fall into a grey area in which features regarded as typical of each category can be found. This, along with an increasing number of reports on the coexistence of the two disorders or on their transformation into one other, has triggered a reexamination of our current understanding and has shed new light on the relationships between HD and NHL. The most interesting and most common example of this relationship is provided by the nodular variant of lymphocyte predominance HD, the so-called *nodular paragranuloma* (NP) according to the terminology introduced by Lennert and Mohri in their classification system for HD in 1974.[1] On the basis of this classification NP was recognized as a distinct clinicopathological entity from the other lymphocyte-predominance subtypes of HD. The presence of lympho-histiocytic cells instead of typical RS cells, the relatively small amount of eosinophils and plasma cells and the less pronounced fibrosis were accepted

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as the main differential histological features; the propensity of NP to progress to large cell NHL, like low-grade follicular lymphomas and unlike other HD subtypes, further accounted for its special place within the HD category. During the last ten years, this view has been strengthened on immunological grounds by the accumulation of evidence consistent with a B-lymphoid phenotype for L&H cells and surrounding lymphocytes. At immunohistochemical analysis, the nodules demonstrate a staining profile similar to germinal centers with expression of B-cell markers that include B1, B4, L26, and J chain rather than the T cell proliferation seen in the most common forms of Hodgkin's disease.[2] In addition, L&H cells rarely display CD15, which is a diagnostic marker for RS cells.[3] On the basis of these features, NP can be regarded as an atypical B-cell proliferation related to HD because of its polymorphic cytological background, and to NHL because of its phenotype and clinical behavior. Thus, due to its overlapping position between HD and NHL, NP prompted many investigators to examine its biological features in order to highlight the nature of its relationship with both disease groups. The first question to be addressed was whether a clonal population of B-cells could be detected in NP. Molecular analysis of the B and T-cell antigen recognition molecules, immunoglobulin and T-cell receptor(s) was successfully used to determine the lineage and the clonality of a variety of NHLs, but not of HD. The absence of molecular rearrangements in HD is usually ascribed to the paucity of the true neoplastic population with respect to the large preponderance of reactive elements. However, a number of cytogenetic studies indicate that a consistent neoplastic clone, as defined by detection of clonal karyotypic abnormalities, does exist in about 50% of the cases evaluated. This observation, coupled with the detection of non-hierarchical Ig rearrangements in sporadic cases, may lead to the hypothesis, assuming the lymphoid nature of the disorder, that the antigen receptor genes in HD might undergo somatic recombination involving regions that are not identified by conventional analysis.

Because of the well-defined B-lymphoid phenotype of NP, the problem of its clonality was first approached by immunohistochemical analysis of Ig light chain expression. No phenotypic restriction has been observed in most of the cases reported in the literature. However, recent improvements in the methods for Ig immunostaining have allowed Schmid et al.,[4] to demonstrate a monotypic Ig light chain on L&H cells in embedded NP specimens, and permitted our lab to detect it on both L&H cells and small lymphocytes in cryostat sections.[5]

Although these features are consistent with the clonal proliferation of B-cells in NP, attempts to demonstrate specific Ig gene rearrangements have been unsuccessful in all our cases but one, in which, in accordance with the l-restricted phenotype, a strong Cl-rearranged band was detected by Southern blot analysis. It is noteworthy that no rearrangements of the heavy chain region could be demonstrated in this case. This unanticipated feature supports the above mentioned hypothesis that in HD and related disorders the mechanisms of the Ig recombination gene may be different from those usually seen in other lymphoid malignancies and, thus, not easily detectable.

The finding of clonal cytogenetic abnormalities in some NP cases without any evidence of expected molecular rearrangements[6] allows us to consider this possibility. Growing knowledge about the biology of HD and related disorders draws attention to their rather uniform pattern at the genetic level, suggesting that each different subtype has a common pathogenetic background despite striking histological and behavioral differences. In this setting, NP belongs to HD category rather than to an ill-defined atypical B-cell hyperplasia. This last assumption is further challenged by the emerging consensus that clonal B-cell proliferation can be demonstrated in NP cases by molecular, immunohistochemical or cytogenetic analysis, accounting for its evolutive potential. The critical step leading from NP to the development of a large cell lymphoma remains unresolved because it is still unclear why NP experiences this type of evolution, which is quite rare among other HD subgroups. It is likely that the presence of an abnormal B-cell population suffering further

neoplastic hits results in the emergence of a fully expanded B-cell clone. The occurrence of mutational event(s) at the Ig level and the acquisition of chromosome changes are probably related to such an evolution as in other neoplastic forms. In addition to its pathogenetic relevance, extensive investigation of the biological features linking NP to large cell NHL has critical diagnostic implications for distinguishing between high and low risk patients, thus allowing an early choice of different therapeutical regimens.

IS THE SO-CALLED T-CELL-RICH B-CELL LYMPHOMA A DISTINCT ENTITY?

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In 1985 Mirchandani et al.[7] described seven cases of B-cell lymphoma that mimicked the morphologic appearance of peripheral T-cell lymphoma. In 1988 Ramsay et al.[8] coined the term *T-cell-rich B-cell lymphoma* (TCRBCL) for such lymphoproliferative disorders. Up to now, more than 100 cases have been reported in the literature. The characteristic feature of TCRBCL is represented by the proliferation of a small number of neoplastic large B-cells amid a predominant population of small T-cells. Several studies by our group and by others have clearly demonstrated the clonal nature of these B-cells and the *reactive* nature of the T-cells.

From a clinical point of view, TCRBCL occurs most frequently in adult patients at both nodal and extra nodal sites (liver, brain, soft tissues, tongue, mediastinum, spleen, bone marrow, etc). Therapeutic protocols are not standardized and the results of different therapies are difficult to compare. Although a poor prognosis had been observed in early reports, a relatively good response to therapy directed at intermediate-grade lymphomas has been reported recently.

In spite of increasing experience in recognizing the histology of this lymphoma, the following points remain unresolved: 1) what are the morphologic and immunophenotypic criteria for identifying TCRBCL? 2) does this condition represent a separate clinico-pathologic entity? 3) how can it be distinguished from peripheral T-cell lymphoma and from Hodgkin's disease?

We will try to answer these questions.

What are the morphologic and immunophenotypic criteria for identifying TCRBCL?

Precise histologic criteria have not yet been defined for TCRBCL. According to various authors, the fraction of reactive T-cells varies from 50 to 90% of the total cellular constituency. Such a large range is a source of diagnostic discrepancies and controversies. In our opinion, the reactive T-cell component should be so preponderant as to simulate a peripheral T-cell lymphoma, with clonal B-cells accounting for less than 10% of the cell population. The large B-cells are individually isolated or aggregated in small nests. They are round, oval or sometimes lobulated. In typical cases there is usually a diffuse pattern of proliferation with complete obliteration of the nodal architecture or, less frequently, interfollicular growth simulating a T-zone lymphoma. A variable number of plasma cells and eosinophils can be observed. Epithelioid histiocytes may also be present and sometimes in such high numbers as to justify the use of the term *histiocyte-rich B-cell lymphoma*.[9] The vascular component is usually well represented.

A detailed immunohistochemical analysis is mandatory. The results on frozen sections can be equivocal because B-cells are rare and light chain restriction is difficult to demonstrate. Immunohistochemical analysis on paraffin sections can be very useful since morphologic and immunophenotypic details are easier to detect,[10] and cytoplasmic light chain restriction is frequently observed in large B-cells.

Molecular analysis can confirm these results by demonstrating immunoglobulin gene rearrangement,[11] provided the neoplastic component is more than 5% of the cell population.

Is it a separate clinico-pathologic entity?

This question is still under debate; however, some observations argue against the distinctiveness of this entity.[12]

Many recurrent cases have been reported to demonstrate the morphology of a large B-cell lymphoma. In one such case we were able to

document the same immunoglobulin gene rearrangement in two biopsies. TCRBCL morphology was also seen in relapses of what was originally a diffuse large B-cell lymphoma, or found to be associated with a morphologically different lymphoma in other sites.

The clinical significance of the accompanying T-cell reaction is uncertain. The high number of these cells rules out the hypothesis that they represent a residual normal population and argues in favor of a transient T-cell reaction. This phenomenon may represent a host immune response to the neoplastic B-cell clone, a theory supported by the observation that the reactive T-cell population tends to diminish when the disease progresses. Alternatively, the effect of some as yet unidentified cytokines secreted by the neoplastic B-cells can be postulated.

Based on these observations, it is likely that TCRBCLs are a heterogeneous group of lymphomas that do not constitute a new entity, but represent a particular presentation of a large B-cell lymphoma.

Differential diagnosis with peripheral T-cell lymphoma and Hodgkin's disease

It is very important for therapeutical purposes to distinguish TCRBCL from peripheral T-cell lymphomas and from Hodgkin's disease (HD) (Table 1).

Peripheral T-cell lymphoma (PTCL). The morphology of TCRBCL may closely resemble PTCL. The predominance of small lymphocytes, frequently associated with numerous endothelial venules, eosinophils, macrophages and plasma cells, is common in TCRBCL, giving a morphological pattern very similar to that observed in PTCLs of low grade malignancy according to the Kiel classification. Although atypical lymphocytes with nuclear irregularities are not seen in TCRBCL, cases containing a spectrum of small and medium-sized lymphocytes (highly suggestive of PTCL) may be observed. In such cases, an incomplete immunohistochemical analysis can be misleading due to the high number of reactive T-cells ($CD3^+$; $CD43^+$; $CD45\ RO^+$). Only a careful examination with a panel of antibodies on fresh and paraffin sections can avoid misdiagnosis.

Hodgkin's disease (HD). Cellular polymorphism and the presence of nuclear lobations in large neoplastic B-cells may resemble mixed cellularity type HD. Nevertheless, these large B-

Table 1. Main differences among T-cell rich B-cell lymphoma (TCRBCL), peripheral T-cell lymphoma (PTCL), lymphocyte predominance Hodgkin's disease (LPHD) and mixed cellularity Hodgkin's disease (MCHD).

	TCRBCL	*PTCL*	*LPHD*	*MCHD*
Reed-Sternberg cells	rare	rare	exceptional	easy to find
Popcorn cells	–	–	easy to find	–
Nodularity	–	–	usually present	–
Phenotype of neoplastic cells on paraffin sections				
CD20	+	–	+	–(°)
CD30	–	-/+(*)	–(**)	+
EMA	–	–	+/–	–
CD15	–	–	–	+
CD3	–	+	–	–/+
CD43	–	+	–	–
CD45RO	–	+	–	–

Abbreviations: +: most, if not all cases positive; +/–: more than 50% of cases positive; –/+: about 25% of cases positive; –: most, if not all cases negative; (°): rare cases positive; (*): a percentage of blasts positive; (**): weak positivity usually observed on frozen sections or on paraffin sections following microwaving.

cells do not possess the big eosinophilic nucleoli that Hodgkin and Reed-Sternberg cells have. The difference between the two processes is facilitated by a panel of antibodies that react with B- and T-cells, including CD15 and CD30. Occasionally, CD20 antibody may be confusing. $CD20^+$ large cells found in paraffin sections of B-cell non-Hodgkin's lymphoma may also be seen in a subset of HD. In the latter, however, this marker tends to show variable expression, possibly related to differences in fixation, processing and staining procedures.

More difficult is the distinction from lymphocyte predominance type HD. If the architectural pattern of HD is nodular (the so-called nodular variant of HD), immunohistochemical analysis basically demonstrates a B-cell rather than a T-cell-rich lesion. Furthermore, a careful search can identify rare typical Reed-Sternberg cells.

In cases of diffuse proliferation (the so-called diffuse variant of HD), the immunophenotype of the lymphoid population is not well defined and the distinction is essentially based on the identification of rare diagnostic Reed-Sternberg cells. A diffuse presentation with generalized disease is not frequent in lymphocyte predominance HD, and is more consistent with a non-Hodgkin's lymphoma. It is possible that some examples of lymphocyte predominance HD with an aggressive course reported in the literature might correspond to TCRBCL.

DO KI-1/CD30 POSITIVE LYMPHOMAS OF THE SKIN REPRESENTS A HOMOGENEOUS GROUP OF TUMORS?

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Introduction

The CD30/Ki-1 antigen

The CD30 antigen is recognized by the monoclonal antibody (MoAb) Ki-1,[13] which reacts with the protein core of a transmembrane glycoprotein, three forms of which – 90, 105, and 120 kDa molecular weight – have been identified by immunoprecipitation.[14] Initially considered to be specific for the Sternberg-Reed (SR) cells of Hodgkin's disease, the CD30 antigen was later found to be expressed on subsets of activated lymphoid B and T cells, as well as on various lymphoma subtypes.[15] Recent studies have made it possible to demonstrate great homology between the CD30 molecule and that of members of the tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor superfamily. The specific ligand for CD30 (CD30L) was identified by means of a recombinant form of the extracellular portion of CD30 on the membrane surface of a stimulated murine T cell clone (7B9).

Furthermore, it has been shown that the C-terminal domain of CD30L shares significant sequence homology with TNF-α, TNF-β, CD27L and CD40.

For these reasons the CD30 molecule is now considered to be another member of the TNF and NGF receptor superfamily.[16]

CD30/Ki-1 antigen expression in malignant lymphomas

Specific anti-CD30 monoclonal antibodies (MoAbs) include Ber-H2 and HRS-4 (both suitable for routine paraffin pathology) and display a wide spectrum of reactivity against neoplastic and non neoplastic cells. Although CD30 is rarely expressed by non-hematolymphoid neoplasms (including embryonal and pancreatic carcinoma), CD30 MoAbs have proved extremely useful for lymphoma subtyping.

CD30 has been detected in most cases of Hodgkin's disease (HD) as well as in various non-Hodgkin's lymphomas (NHLs).

Among this latter group the Ki-1 antigen identifies a distinct type of high grade lymphoma that is designated either as anaplastic large cell lymphoma (ALCL) or as Ki-1/CD30-positive (large cell) lymphoma (LCL).[16]

Besides the ALCL group, CD30 may also be expressed by other NHL subtypes with non-anaplastic cytology, such as follicular-derived and immunoblastic B cell lymphomas, as well

Table 2. Clinical and histological differences between lymphomatoid papulosis (LyP) and primary cutaneous CD30+ large-cell lymphomas (CLCLs), including regressing atypical histiocytosis.

	Lyp	*Primary CD30+ CLCLs*
Type of skin lesions	papule	nodule/tumor
Extent of skin lesions	generalized	solitary
Spontaneous regression	always	rare
Histology		
– CD30+ cells	dispersed	large sheets
– inflammatory cells	abundant	few / moderate
– dermal infiltrate	superficial	deep
Phenotypic profile	T cell markers	T, B, or null
Progression to systemic lymphoma	less than 5%	25%
Clinical behavior	favorable	better than primary nodal large-cell CD30+ NHLs

as AILD, pleomorphic medium, large and immunoblastic T cell malignancies.[17]

In addition, the so-called *small-cell predominant variant of Ki-1 (CD30)+ T-cell lymphoma* has been described very recently in the literature.[18] This finding confirms the need for distinguishing between anaplastic and non-anaplastic CD30+ cytologic subtypes.

CD30 positive lymphoproliferative disorders of the skin

The presence in the skin of CD30 characterizes a wide spectrum of lymphoproliferative diseases that can be subdivided into three major groups (Table 2). The first group consists of primary cutaneous lymphoproliferative disorders and includes primary cutaneous CD30+ lymphomas, rare cases of primary cutaneous Hodgkin's disease, as well as ambiguous entities like *regressing atypical histiocytosis* (RAH) and *lymphomatoid papulosis* (LyP), the latter two possibly being related to ALCLs and HD.

The second group includes cutaneous lymphomas that have progressed from other types of cutaneous lymphomas (e.g. mycosis fungoides).

The third group comprises cases of skin involvement in the course of primary extracutaneous CD30+ lymphomas or Hodgkin's disease.

The present commentary focuses mainly on primary CD30+ cutaneous lymphoproliferative disorders.

Primary cutaneous CD30-positive lymphoproliferative disorders

Primary cutaneous CD30+ lymphomas

It has been firmly established in recent years that the CD30+ lymphomas described in lymph nodes can also present primarily in the skin.[19] Analogously to their nodal counterparts, primary cutaneous CD30+ lymphomas have been defined on the basis of morphology (i.e. anaplastic cytology) and/or immunophenotype (expression of the CD30 molecule), and have been designated accordingly as anaplastic large cell lymphomas or Ki-1 (CD30) positive lymphomas. However, there is still confusion regarding the definition and terminology of these malignancies. For these reasons, in a recently published study,[20] we suggest that the definition of primary cutaneous CD30+ lymphomas should be restricted to those cases which meet the following criteria:

a. expression of CD30 in at least 75% of the neoplastic cells;
b. no evidence of lymphomatoid papulosis;
c. no history of concurrent LyP, mycosis fungoides or other type of primary cutaneous lymphoma;

d. no extracutaneous localization at presentation.

Clinically, most patients with this type of cutaneous malignancy present with a solitary or localized skin lesion, which may consist of one to several papules, nodules, small tumors or, frequently, an ulcerating tumor. In rare cases, patients present with several scattered nodular skin lesions that are not confined to one anatomical area. Remarkably, in some patients the skin lesions tend to regress spontaneously.

Histologically this group of cutaneous lymphomas contains $CD30^+$ ALCLs as well as cases of non-anaplastic cytology (i.e. immunoblastic, medium and large T-cell subtypes). Most $CD30^+$ primary cutaneous lymphomas show a T-cell phenotype with a variable loss of T-cell antigens (i.e. CD2 and CD3); they strongly express CD30 and other activation antigens, but generally do not express CD15. Recent studies have stressed the possibly favorable prognostic value of CD30 expression in these cutaneously confined diseases, and have revealed no differences in clinical presentation or prognosis between anaplastic and non-anaplastic cytology subtypes.[20] The fact that $CD30^+$ lymphoma patients survive better than primary node-based or extranodal non-cutaneous $CD30^+$ patients suggests a possible prognostic role for the primary site in predicting the clinical outcome of these malignancies.[21,22]

Regressing atypical histiocytosis

Regressing atypical histiocytosis (RAH), which was originally described by Flynn et al.,[23] is characterized by rapidly evolving nodulo-ulcerative lesions that show dermal infiltration in the form of strikingly atypical, large histiocytoid cells with a histologically malignant appearance. Most RAH patients have a protracted benign course, but the literature has recently reported possible lymph node involvement and progression to systemic lymphomas. The term RAH was originally suggested as a result of morphological and histochemical studies. At present we must stress that *histiocytoid* RAH cells are cytologically indistinguishable from the atypical tumor cells of ALCL. In addition, recent immunohistochemical and molecular biology investigations demonstrated the T-cell lineage of atypical RAH cells. For these reasons we recommend that these cases be classified as ALCLs, and that the confusing term RAH be avoided.

Primary cutaneous Hodgkin's disease

Cutaneous lesions occur in 10%-50% of patients with Hodgkin's disease.[24] In most cases patients present with nonspecific manifestations that include pruritus and herpes zoster. In addition, other conditions may be found: urticaria, erythema nodosum, ichthyosis, dermatomyositis, etc. Specific secondary cutaneous lesions in HD are somewhat less common, while primary HD cases are exceptionally rare. A diagnosis of primary cutaneous HD requires caution and extensive investigation to exclude extracutaneous manifestations. The histological features of primary cutaneous HD are similar to those of lymph nodes. The most frequent histological subtypes are: mixed cellularity, nodular sclerosis and lymphocyte depletion, this last group includes cases that are not easily distinguishable from ALCL. Sternberg-Reed and HD usually display a $CD15^+$, $CD30^+$, $CD45^-$ phenotype, which may be of some value in attempts to differentiate HD infiltrate from $CD30^+$ ALCL.

Lymphomatoid papulosis

Lymphomatoid papulosis was originally defined by Macaulay in 1968[25] as a continuing, self-healing eruption that is clinically benign, but histologically suggestive of a malignant lymphoma. Patients are generally middle-aged or elderly adults who have erythematous scales, non pruritic papules whose appearance on the body surface is random except that they tend to spare the face, the palms and the soles. These lesions (generally under 2 cm in diameter) follow a distinctive 4 to 6-week course: after appearance, they become hemorrhagic and necrotic and then regress leaving hyperpigmented scars. LyP patients usually have a prolonged but essentially benign clinical course. Recent studies have revealed that the risk of an individual LyP patient developing systemic lymphoma is less than 5%. Like the clinical

lesions, the histology varies in appearance depending on the stage of development. The earliest erythematous papules have a superficial and deep perivascular lymphoid infiltrate that contains some enlarged and hyperchromatic lymphocyte nuclei. Eosinophils and plasma cells are absent in the early phase. In the mid, or well-developed phase the lesions have a characteristic wedge-shaped appearance. The lymphocytic infiltrate is superficial and perivascularly arranged. It contains large atypical lymphoid cells admixed with scattered CD30$^+$ cells, the latter being cytologically indistinguishable from Sternberg-Reed cells and their variants. Neutrophils usually appear in this phase, but eosinophils are uncommon.

Willemze et al.[26] proposed a subdivision of LyP into two groups, respectively designated type A and type B. Type A has the above described histological appearance. Type B LyP has few to very few of the large atypical cells and is predominantly composed of small to medium-sized T-lymphocytes with convoluted nuclei. Immunophenotypic studies demonstrated that LyP lesions contain many CD4$^+$ T cells. The large atypical cells express CD30 and other activation antigens and in some cases, the CD15/antigen. The cytological and immunophenotypical similarities between the large atypical cells and the neoplastic cells of cutaneous CD30$^+$ ALCL, along with the quite favorable clinical behavior of both these CD30$^+$ disorders, suggests a close relationship between the two conditions.[27]

Conclusions

There is considerable clinical, morphological and functional overlapping between primary cutaneous CD30$^+$ lymphomas, RAH, LyP and HD. This strongly suggests that these entities represent a continuous spectrum of CD30$^+$ lymphoproliferative disorders. In addition, cases of LyP have recently been included in series previously published as CD30-positive ALCL, which indicates that at least some investigators no longer make this distinction. However, differences do exist, particularly as regards the frequency of spontaneous regression and the risk of developing systemic lymphomas. So it is still important to distinguish among these conditions, especially in order to avoid overtreating patients, which results in unnecessary toxicity. Much has been written on CD30$^+$ cutaneous lymphoproliferative disorders, but considerable confusion persists regarding their proper classification. This confusion is mainly due to the limited number of cases investigated and the lack of uniform clinical and histological criteria in previous studies. Additional research is necessary to provide detailed and fully acceptable clinical and pathologic criteria for the diagnosis of CD30$^+$ cutaneous lymphomas and related disorders.

DOES ANAPLASTIC LARGE CELL LYMPHOMA INCLUDE DISTINCT CLINICO-PATHOLOGIC SUBTYPES?

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Anaplastic large cell (ALC) lymphoma, an entity that has attracted the attention of most pathologists over the last few years, was first described in 1985 in a now-famous paper by Stein et al.[15] as a lymphoid tumor consisting of large, bizarre cells which express the lymphoid activation antigen detected by the monoclonal antibody (MoAb) Ki-1. In their paper the authors underlined that in the past ALC lymphoma had often been misdiagnosed as malignant histiocytosis or lymph node metastatic involvement from undifferentiated carcinoma or melanoma of unknown primary site.

In spite of the terminology used by Stein et al.,[15] the neoplasm quickly became popular in the literature as the *Ki-1 cell lymphoma*, a name, however, which refers to the tumor's phenotype rather than its morphology. In order to avoid any confusion with Hodgkin's disease (HD) and other lymphoid tumors that also express the Ki-1/CD30 molecule, the term ALC lymphoma was officially included in updated classi-

fication schemes in 1988.[28] Despite the fact that tumor is diagnosed regularly homogeneous criteria are not employed, as can be seen from the reports of Chan et al.[29] and Chott et al.,[30] who both described morphological varieties of it.

The possibility of a subclassification of ALC lymphomas was clearly illustrated at two workshops held in 1987 and 1988 at the Pathology Istitute of the Berlin Free University.[31,32] At these two events, criteria were defined for recognizing four separate varieties of ALC lymphoma, namely the common, giant-cell rich, Hodgkin-related and lymphohistiocytic subtypes[31,32] (Table 3).

ALC lymphoma, common type is characterized by a neoplastic growth consisting of large cells having a moderate amount of cytoplasm that turns greyish-violet at Giemsa staining. Their nuclei show variable profiles (round, oval, kidney-shaped), rather dispersed chromatin and prominent nucleoli that sometimes take on an inclusion-like appearance. Some Reed-Sternberg-like cells are usually observed, and mitotic figures are numerous. The neoplastic cells tend to diffuse sinusoidally, giving rise to wide, solid sheets.

The giant-cell rich subtype differs from the common type for the frequent occurrence of multinucleated giant cells, often reminiscent of the diagnostic cells of HD.

In the lymphohistiocytic subtype,[33] tumoral elements having the same cytological features as those of the common type are mixed with a large number of benign-looking macrophages of peculiar morphology (eccentric nuclei with dense chromatin and wide rims of acidophilic cytoplasm). These elements overwhelm the neoplastic component, do not express the proliferation-associated nuclear antigen Ki-67, and are quite likely attracted by cytokines released by lymphomatous cells.

The Hodgkin-related subtype is the most controversial of the varieties, and owing to the difficulties involved in detecting it and in the differential diagnosis with HD, it will be discussed in greater detail. According to the criteria contained in a proposal for a consensus international classification of malignant lymphomas, which reflects the ideas of 19 American and European hematopathologists,[34] at light microscopy examination the tumor is characterized by large cells with staining characteristics (clear cytoplasm at both H&E and Giemsa staining) that differ from those observed in the common type. These elements tend to a cohesive growth, and most often give rise to nodules that may be

Table 3. Main differences among anaplastic large-cell lymphoma subtypes.

	CT	*HR*	*GCR*	*LH*
Neoplastic cells:				
Mononucleated	prevalent	prevalent	variable	rare
Giant multinucleated (Reed-Sternberg-like)	rare	easy to find	prevalent	rare
Nuclear shape	———	horseshoe/kidney-shaped	———	
Cytoplasm (Giemsa)	greyish-violet	clear	greyish-violet	greyish-violet
Intrasinusoidal diffusion	prominent	———	present	———
Nodular aggregation	possible	prominent	possible	rare
Fibrosis	rare	evident	rare	rare
Reactive macrophages	rare	rare	rare	prominent

Abbreviations: CT: Common type; HR: Hodgkin's related; GCR: Giant-cell rich; LH: Lymphohistiocytic

surrounded by fibrotic collagen bands.

The fact that nodularity and fibrosis are two morphological features that the Hodgkin-related variety of ALC lymphoma shares with nodular sclerosing HD illustrates the difficulty in tracing the confines between these two entities. Intrasinusoidal diffusion is usually observed in Hodgkin-related ALC lymphoma and can be of help in the differential diagnosis with HD, where it represents a very rare finding. At phenotypical analysis,[32,34] the elements of Hodgkin-related ALC lymphoma show the same molecular expression as the common type ($CD30^+$, $CD45^{+/-}$, $EMA^{+/-}$, $CD15^{-/+}$, T-cell markers in about 50% of cases, B-cell markers in another 20%, null phenotype in roughly 30%, and hybrid phenotype in 1-2%). Regarding phenotype, very little is known; no studies have yet been reported on the t(2;5) translocation that is observed frequently in ALC lymphoma, common type, of T-cell derivation.[32]

Preliminary data on integration of the Epstein-Barr virus (EBV) show that it is present in the genoma of tumoral cells in about 17% of cases of the Hodgkin-related subtype. This finding is quite similar to that observed in ALC lymphoma, common type (16-18% of cases), while it differs significantly from the percentage reported in HD, where EBV is integrated in the genoma of Hodgkin and Reed-Sternberg cells in 60-85% of cases.[32] Thus, this factor could represent a further element for differentiating the two pathologies.

Acccording to findings collected during an Italian trial on high-grade non-Hodgkin lymphomas (NHLs) held between August 1988 and August 1991,[35] which permitted 69 ALC lymphomas to be identified and homogeneously treated, the Hodgkin-related subtype showed distinctive clinical features that differed slightly from those of the common type. In particular, these patients were young adults (mean age 27 yrs), most often presented in stage II (67.8%), and always had a mediastinal mass with frequent bulky disease (57.1%).

On the other hand, in the common type mean age was 33.4 yrs, stage distribution was much broader, and mediastinal mass occurred in only 58.5% of cases, with bulky disease being observed in only 24.4%.

Employment of third generation chemotherapy regimens in the trial permitted similar rates of complete remission (CR) in the Hodgkin-related and common types of ALC lymphoma (68.4% and 67.8%, respectively). These results did not differ from those observed in the remaining 220 high-grade NHLs of different histology enrolled in the same protocol (68% CR). It is noteworthy that patients with the Hodgkin-related subtype of ALC lymphoma tended to maintain CR more easily than those with the common type (80% vs. 68% at 54 months). Despite these encouraging findings, there is no general agreement as to the optimal treatment of the Hodgkin-related subtype, and studies are needed to compare the effectiveness of third generation chemotherapy regimens for high-grade NHLs vs. standard protocols for HD (MOPP and/or ABVB). Furthermore, careful evaluation is required regarding the possibility of including the recently generated Ber-H2 saporin-6 immunotoxin[36] among the therapeutic tools, especially as far as eradication of residual disease following conventional chemotherapy is concerned.

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WHICH SUBTYPES OF HODGKIN'S DISEASE MIGHT BE INCLUDED AMONG ANAPLASTIC LARGE CELL LYMPHOMAS?

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The close morphological and phenotypical similarities between the neoplastic cells of anaplastic large cell lymphoma (ALCL) and those of Hodgkin's disease (HD) have recently raised two crucial questions involving possible pathogenetic relationships between the two entities and the histological criteria that would permit a precise differential diagnosis. This also

has practical relevance, mainly because of the substantially different prognostic and therapeutic implications of the two forms. The original classification of HD proposed in the Rye Conference[37] distinguished four main histological variants (lymphocyte predominance, nodular sclerosis, mixed cellularity and lymphocyte depletion) and is still used worldwide. As far as ALCL is concerned, this entity has been subdivided more recently, following its initial description,[28] into four histological subtypes, namely common, Hodgkin-related, giant-cell rich, and lymphohistiocytic.[32]

At present, there is increasing evidence that some cases of HD previously diagnosed as nodular sclerosis (HD-NS) and/or lymphocyte depletion (HD-LD) variants might be considered within the morphological spectrum of ALCL.

As far as HD-LD is concerned, it seems conceivable that most cases of the so-called *sarcomatous reticular* subtype of HD-LD might now be classified as ALCL, whereas the rare cases of HD-LD with *diffuse fibrosis* may still retain their original histological definition.

With regard to Hodgkin's disease, nodular sclerosis variety, there is some evidence that a few definite cases of this variant might currently be considered as ALCL, Hodgkin-related (ALCL-HR) subtype. These cases would have been previously classified as HD-NS grade II and HD-NS the so-called *syncytial* variant. HD-NS grade II is substantially featured by the presence of numerous bizarre, anaplastic-appearing Hodgkin's cells, with or without depletion of lymphocytes. These cells have large hyperchromatic nuclei with prominent nucleoli and are different from the typical *lacunar* cells of the conventional HD-NS.[38] According to MacLennan and the British National Lymphoma Investigation,[38] HD-NS grade II is associated with poor response to initial therapy, increased relapse rate and decreased survival as compared with conventional (grade I) HD-NS. The therapeutic implication of these findings is that HD-NS grade II should require more aggressive initial therapy.[38] Interestingly enough, the viewpoints of MacLennan et al. have recently been disputed by Masih et al., who showed that histological grade (I or II) did not really predict the clinical outcome of advanced-stage (bulky stage II, stage III and stage IV) HD-NS in a group of selected patients who had received well-standardized, homogeneous treatment.[39] Thus, the prognostic implications of dividing HD-NS into low-grade (grade I) and high-grade (grade II) histological subtypes are as yet unclear and still a matter of further investigation.

The term *syncytial* variant of HD-NS was originally proposed by Strickler et al.[40] to describe cases with the architectural features of HD-NS, in which numerous Reed-Sternberg cell variants were observed to be arranged in sheets and cohesive clusters. These authors pointed out the importance of a correct differential diagnosis between this peculiar form of HD-NS and metastatic tumors (carcinoma, melanoma), thymoma and large cell non-Hodgkin lymphoma. However, they did not report on the clinicopathologic correlations of the *syncytial* variant of HD-NS. A comparison of the histology of HD-NS grade II with that of the *syncytial* variant of HD-NS reveals the close analogies between these two forms, as well as the similarities between both of them and the Hodgkin-related subtype of ALCL. It is therefore very likely that a substantial number of cases of HD-NS considered as grade II or as *syncytial* variants would now be regarded as ALCL-HR. As a matter of fact, the boundaries between HD and ALCL may be somewhat vague in such instances, with the main difference still being that ALCL is substantially composed of neoplastic cells with anaplastic morphology, whereas HD shows a lower number of cells with a similar morphologic appearance within a more abundant background of reactive cells.

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References

1. Lennert K, Mohri N. Histologische Klassifizierung und Vorkommen des Morbus Hodgkin. Internist 1974; 15:57-65.
2. Hansmann ML, Wacker HH, Radzun HJ. Paragranuloma is a variant of Hodgkin's disease with predominance of B cells. Virchows Arch (A) 1986; 409:171-81.
3. Burns BF, Colby TV, Dorfman RF. Differential diagnostic features of nodular L&H Hodgkin's disease, including pro-

gressive transformation of germinal centers. Am J Surg Pathol 1984; 8:253-61.
4. Schmid C, Sargent C, Isaacson PG. L and H cells of nodular lymphocyte predominant Hodgkin's disease show immunoglobulin light chain restriction. Am J Pathol 1991; 139:1281-9.
5. Kerim S, Reato G, Abele C, et al. Immunoglobulin light chain restriction and clonal rearrangement in nodular paragranuloma. Report of a case. Leuk Lymphoma, in press.
6. Kerim S, Bonavolontà MR, Abele C, Reato G, Valente G, Palestro G. Clonal cytogenetic abnormalities can be detected in nodular paragranuloma (Abstract). Cancer Detect Prev 1993; 17:58.
7. Michandani I, Palutke M, Tabaczka P, Goldfarb S, Eisenberg L, Pak MS. B-cell lymphomas morphologically resembling T-cell lymphomas. Cancer 1985; 56:1578-83.
8. Ramsay AD, Smith W, Isaacson P. T-cell-rich B-cell lymphoma. Am J Surg Pathol 1988; 12:433-43.
9. Delabie J, Vandenberghe E, Kennes C, et al. Histiocyte-rich B-cell lymphoma. A distinct clinicopathologic entity possibly related to lymphocyte predominant Hodgkin's disease, paragranuloma subtype. Am J Surg Pathol 1992; 16:37-48.
10. Osborne BM, Butler JJ, Pugh WC. The value of immunophenotyping on paraffin sections in the identification of T-cell rich B-cell large-cell lymphomas: lineage confirmed by JH rearrangement. Am J Surg Pathol 1990; 14:933-8.
11. Scarpa A, Bonetti F, Zamboni G, Menestrina F, Chilosi M. T-cell-rich B-cell lymphoma. Am J Surg Pathol 1989; 13:335-7.
12. Rodriguez J, Pugh W, Cabanillas F. T-cell-rich B-cell lymphoma. Blood 1993; 82:1586-9.
13. Schwab U, Stein H, Gerdes J, et al. Production of a monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. Nature 1982; 299:65-7.
14. Froese P, Lemke H, Gerdes J, et al. Biochemical characterization and biosynthesis of the Ki-1 antigen in Hodgkin-derived and virus transformed human B and T lymphoid cell lines. J Immunol 1987; 139:2081-7.
15. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985; 66:848-58.
16. Dürkop H, Latza U, Hummel M, et al. Molecular cloning and expression of a new member of the nerve growth receptor family that is characteristic of Hodgkin's disease. Cell 1992; 68:421-7.
17. Piris M, Brown DC, Gatter KC, et al. CD30 expression in non-Hodgkin's lymphoma. Histopathology 1990; 17:211-8.
18. Kinney MC, Collins RD, Greer JP, et al. A small-cell predominant variant of primary K-1 (CD30)+ T-cell lymphoma. Am J Surg Pathol 1993; 17:859-68.
19. Morra E, Rosso R, Lazzarino M, et al. Adult Ki-1-positive large cell anaplastic lymphoma presenting with skin lesions. Acta Haemat 1989; 81:51-5.
20. Beljaards RC, Kaudewitz P, Berti E, et al. Primary cutaneous CD30-positive large cell lymphomas: definition of a new type of cutaneous lymphoma with a favorable prognosis. Cancer 1993; 71:2097-104.
21. De Bruin PC, Beljaards RC, Van Heerde P, et al. Differences in clinical behavior and immunophenotype between primary cutaneous and primary nodal anaplastic large cell lymphoma of T-cell or null cell phenotype. Histopathology 1993; 23:127-35.
22. Paulli M, Rosso R, Kindl S, et al. Primary gastric CD30-(Ki-1)-positive large cell non-Hodgkin's lymphomas. A clinicopathologic analysis of six cases. Cancer 1994; 73:541-9.
23. Flynn KJ, Dehner LP, Gajl-Peczalska KJ, et al. Regressing atypical histiocytosis: a cutaneous proliferation of atypical neoplastic histiocytes with unexpectedly indolent biologic behavior. Cancer 1982; 49:959-70.
24. Burg G, Braun-Falco O. Cutaneous lymphoma, pseudolymphomas and related disorders. Berlin: Springer, 1993.
25. Macaulay WL. Lymphomatoid papulosis: a continuing, self-healing eruption, clinically benign-histologically malignant. Arch Dermatol 1968; 97:23-30.
26. Willemze R, Meyer CJLM, Van Vloten WA, et al. The clinical and histological spectrum of lymphomatoid papulosis. Br J Dermatol 1982; 107:131-44.
27. Kadin ME. The spectrum of Ki-1$^+$ cutaneous lymphomas. Curr Probl Dermatol 1990; 19:132-43.
28. Stansfeld AG, Diebold J, Kapanci Y, et al. Updated Kiel classification for lymphomas. Lancet 1988; i:292-3.
29. Chan JKC, Hui PK, Leungs TW, Lau WH, McGuire LJ. Anaplastic large cell Ki-1 lymphoma: delineation of 2 morphological types. Histopathology 1989; 15:11-34.
30. Chott A, Kaserer K, Augustin I, et al. Ki-1-positive large cell lymphoma. A clinicopathologic study of 41 cases. Am J Surg Pathol 1990; 14:439-48.
31. Stein H, Gerdes J, Tippelmann G, et al. Ki-1 lymphoma: experimental and clinical findings. Abstract book. Third International Conference on Malignant Lymphoma, Lugano, 1987.
32. Stein H, Herbst H, Anagnostopoulos I, Niedobitek G, Dallenbach F, Kratzsch H-C. The nature of Hodgkin and Reed-Sternberg cells, their association with EBV, and their relationship to anaplastic large cell lymphoma. Ann Oncol 1991; 2:33-8.
33. Pileri S, Falini B, Delsol G, et al. Lymphohistiocytic T-cell lymphoma (anaplastic large cell lymphoma CD30$^+$/Ki-1$^+$ with a high content of reactive histiocytes). Histopathology 1990; 16:383-91.
34. Harris NL, Jaffe ES, Stein H, et al. Proposal for an international consensus on the classification of lymphomas. Blood 1994; in press.
35. Pileri S, Bocchia M, Baroni CD, et al. Anaplastic large cell lymphoma (CD30$^+$/Ki-1$^+$): results of a prospective clinicopathologic study of 69 cases. Br J Haematol 1994; 86:513-23.
36. Falini B, Bolognesi A, Flenghi L, et al. Response of refractory Hodgkin's disease to therapy with anti-CD30 monoclonal antibody linked to saporin (Ber-H2-SO6 immunotoxin). Lancet 1992; i:1195-7.
37. Lukes RJ, Craver LF, Hall TC, et al. Report of the Nomenclature Committee. Cancer Res 1966; 26:1311.
38. MacLennan KA, Bennett, MH, Tu A, et al. Relationship of histopathologic features to survival and relapse in nodular sclerosing Hodgkin's disease. A study of 1659 patients. Cancer 1989; 64:1686-93.
39. Masih AS, Weisenburger DD, Vose JM, et al. Histologic grade does not predict prognosis in optimally treated, advanced-stage nodular sclerosing Hodgkin's disease. Cancer 1992; 69: 228-32.
40. Strickler JG, Michie SA, Warnke RA, Dorfman RF. The "syncytial" variant of nodular sclerosis Hodgkin's disease. Am J Surg Pathol 1986; 10:470-7.