Classification of T-cell and NK-cell neoplasms based on the REAL classification*

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Summary

Mature or peripheral T-cell lymphomas are uncommon, accounting for only 10%-15% of all non-Hodgkin's lymphomas. The classification of these neoplasms has been controversial. In contrast to B-cell lymphomas, cytologic grade has not been very useful in predicting the clinical course. This finding may result from the generally aggressive clinical course associated with T-cell lymphomas. Prior studies have suggested that stage of disease may be more important than cytologic subtype.

Clinical presentation is very important in the classification of T-cell malignancies. For T-cell lymphomas, cytologic features alone are not sufficient to distinguish among disease entities. For example, adult T-cell leukemia/lymphoma (ATLL) often cannot be distinguished morphologically from HTLV-1-negative T-cell lymphomas. Most extranodal T-cell lymphomas appear to be derived from cytotoxic T cells, which express perforin, TIA-1, and granzyme B. Three broad groups of T-cell malignancies can be identified: (1) leukemic or systemic disease; (2) nodal disease; (3) extranodal disease. Anaplastic large-cell lymphoma (ALCL) is probably the single most common subtype of T-cell lymphoma. Classical ALCL should be distinguished from primary cutaneous ALCL (CD30+ lymphoproliferative disease of the skin), which is a distinct disease entity.

Key words: cytotoxic T cells, T-cell lymphoma

Introduction

While the definition of precursor T-cell or lymphoblastic neoplasms is straightforward, the classification of peripheral T-cell lymphomas has been controversial. Most previously published classification schemes for the malignant lymphomas published in the United States or Europe have been based on B-cell malignancies, as these are far more common than their T-cell counterparts. The Rappaport classification and the original Kiel and Lukes-Collins classifications focus primarily on B-cell lymphomas. The Working Formulation (WF), being based on the Rappaport scheme, also focuses almost exclusively on B-cell malignancies. Only mycosis fungoides is delineated as a specific entity, and it is included in the miscellaneous category. The vast majority of peripheral T-cell lymphomas in the WF are classified as either diffuse, mixed, small, and large cell or large-cell immunoblastic. T-cell lymphomas composed predominantly of small atypical cells would be included in the diffuse small cleaved-cell category or remain unclassified.

The revised Kiel classification does include T-cell lymphomas [1, 2]. However, the ILSG classification differs from the approach utilized in the Kiel scheme in several respects (Table 1). For one, the ILSG classification recognizes adult T-cell leukemia/lymphoma (ATLL) as a distinct clinicopathologic entity [3]. The Kiel classification describes T-cell lymphomas in morphologic terms and notes independently the status as HTLV-1 positive or negative (Table 2).

The Kiel classification divides T-cell lymphomas into low-grade and high-grade forms based on the cytologic features of the neoplastic cells. Low-grade lymphomas are composed of small- to medium-sized atypical cells, whereas larger cells are more common in the high-grade lymphomas. While these distinctions are valid cytologically, they do not necessarily relate to a more aggressive clinical course for the high-grade lesions [4]. For this reason, the ILSG classification does not divide T-cell lymphomas into low-grade and high-grade variants.

Additionally, T-zone lymphoma and lymphoepithelioid-cell lymphoma were not felt to be distinct clinico-

Table 1. Post-thymic T-cell and NK-cell neoplasms in the REAL scheme.*

<table>
<thead>
<tr>
<th>Predominantly leukemic malignancies</th>
<th>Predominantly nodal malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cell CLL/PLL</td>
<td>Peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>Large granular lymphocyte leukemia: T and NK</td>
<td>Angioimmunoblastic T-cell lymphoma (AILD-like)</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma (HTLV-1+)a</td>
<td>Anaplastic large cell lymphoma (T and null cell)</td>
</tr>
<tr>
<td>Predominantly extranodal malignancies</td>
<td>Predominantly extranodal malignancies</td>
</tr>
<tr>
<td>Mycosis fungoides/Sézary syndrome</td>
<td>CD30+ lymphoproliferative disease (cutaneous ALCL)</td>
</tr>
<tr>
<td>Intestinal T-cell lymphoma</td>
<td>Angiocentric NK/T-cell lymphoma</td>
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<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>Hepatosplenic γδ T-cell lymphoma</td>
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</tbody>
</table>

a Diseases are grouped according to clinical presentation; ATLL may be leukemic or lymphomatous.

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pathologic entities, although they do represent morphologic variations that can be seen in peripheral T-cell lymphoma. Previous studies have suggested that these variants are difficult to reliably distinguish from other nodal T-cell lymphomas [5]. Cytogenetic studies also have suggested overlap among these categories of low-grade T-cell lymphoma in the Kiel classification [6]. Therefore, they were left within the category peripheral T-cell lymphomas, unspecified (Table 3).

The ILSG classification also recognizes the distinctive nature of many extranodal T-cell lymphomas (Table 4). These include the nasal and nasal-type angiocentric lymphomas, enteropathy-associated T-cell lymphoma, and subcutaneous panniculitic T-cell lymphoma. Clinical features play an important role in the definition of many T-cell lymphoma entities, as it is felt that cytologic features alone are not sufficient to delineate many of these diseases. The following review summarizes the REAL classification, as it deals with T-cell lymphomas. T-cell leukemias and mycosis fungoides are not included.

Peripheral T-cell lymphoma (PTL), unspecified

Provisional cytologic subtypes: medium-sized cell, mixed medium and large cell, large cell; lymphoepithelioid cell.

WF: diffuse small cleaved, diffuse mixed small and large cell, large-cell immunoblastic.

Kiel: T-zone lymphoma; lymphoepithelioid-cell lymphoma; pleomorphic small, medium, and large cell (HTLV-1 negative); immunoblastic (HTLV-1 negative).

PTLs account for only 10%-15% of all non-Hodgkin's lymphomas. Angioimmunoblastic T-cell lymphoma is the most common specific form. The majority of other PTLs arising in lymph nodes would fall in the unspecified category. PTLs are characterized by a heterogeneous cellular composition. There is usually a mixture of small and large atypical lymphoid cells. An inflammatory background is frequent, consisting of eosinophils, plasma cells, and histiocytes. If the epithelioid histiocytes are numerous and clustered, it fulfills criteria for lymphoepithelioid cell lymphoma or Lennert's lymphoma [7, 8]. In the ILSG classification lymphoepithelioid-cell lymphoma was considered a morphologic variant of PTL and not a distinctive clinico-pathologic entity. It has not been associated with any immunophenotypic, cytogenetic, or molecular features permitting distinction from other PTLs [6].

PTL may show preferential involvement of the paracortical region of lymph nodes. In some cases, this architectural pattern is striking, with sparing of follicles. Such cases have been referred to as T-zone lymphoma [1]. However, on cytologic grounds, they resemble other peripheral T-cell lymphomas of medium or mixed cytologic types. The neoplastic cells usually have a moderate amount of pale cytoplasm. A conspicuous clear-cell component is more characteristic of angioimmunoblastic T-cell lymphoma than PTL, unspecified.

Clinically, PTLs present in adults. Most patients exhibit generalized lymphadenopathy, hepatosplenomegaly, and frequent bone marrow involvement. Constitutional symptoms, including fever and night sweats, are common, as is pruritus. The clinical course is aggressive, although complete remissions may be obtained with combination chemotherapy [9-11]. However, the relapse rate is higher in PTLs than in B-cell lymphomas of comparable histologic grade [11].

PTL, as defined in the ILSG classification, is heterogeneous. It is likely that individual clinico-pathologic entities will be delineated in the future from this broad group of malignancies. Thus far, immunophenotypic criteria have not been helpful in delineating subtypes. Most cases have a mature T-cell phenotype and express one of the major subset antigens: CD4 > CD8. These are not clonal markers, and antigen expression can change over time. Deletion of one of the pan T-cell antigens (CD3, CD5, CD2, or CD7) is seen in 75% of cases, with CD7 most frequently being absent [12].
**Angioimmunoblastic T-cell lymphoma (AILD)**

WF: diffuse mixed small and large cell, large-cell immunoblastic.

Kiel: angioimmunoblastic.

AILD was initially proposed as an abnormal immune reaction or form of atypical lymphoid hyperplasia with a high risk of progression to malignant lymphoma [13]. Because the majority of cases show clonal rearrangements of T-cell receptor genes, it is now regarded as a variant of T-cell lymphoma [14]. The median survival is generally less than five years, so that the designation as lymphoma is warranted on clinical grounds [15].

The nodal architecture is generally effaced, but peripheral sinuses are often open and even dilated. The abnormal infiltrate usually extends beyond the capsule into the surrounding adipose tissue. Hyperplastic germinal centers are absent. However, there may be regressed follicles containing a proliferation of dendritic cells and blood vessels. These regressed follicles are referred to as 'burned out'.

At low power, there is usually a striking proliferation of postcapillary venules with prominent arborization. The cellularity of the lymph node usually appears reduced or depleted at low power. Clusters of lymphoid cells with clear cytoplasm may be seen. Their nuclei exhibit moderately condensed chromatin and a slightly irregular nuclear contour. These are admixed with a polymorphous cellular background containing small normal-appearing lymphocytes, basophilic immunoblasts, plasma cells, and histiocytes, with or without eosinophils. The abnormal cells are usually CD4+ T cells. In paraffin sections, a helpful diagnostic feature is the presence of numerous CD21+ dendritic reticulum cells, which are especially prominent around postcapillary venules [16]. Polyclonal plasma cells may be numerous.

AILD presents in adults. Most patients have generalized lymphadenopathy and prominent systemic symptoms with fever, weight loss, and skin rash. There is usually a polyclonal hypergammaglobulinemia. Patients may respond initially to steroids or mild cytotoxic chemotherapy, but progression usually occurs. More aggressive combination chemotherapeutic regimens have led to a higher remission rate, but patients are prone to secondary infections with cytomegalovirus. The acute form of the disease is associated with a poor prognosis and a median survival of under two years [25]. Complete remissions may be obtained but the relapse rate is nearly 100%.

Chronic and smoldering forms of the disease are seen less commonly [27]. These are associated with a much more indolent clinical course. There is usually minimal lymphadenopathy. The predominant clinical manifestation is skin rash, with only small numbers of atypical cells in the peripheral blood. In the chronic and smoldering forms, HTLV-1 virus is also found integrated within the atypical lymphoid cells.

The cytologic spectrum of ATLL is extremely diverse. The cells may be small with condensed nuclear chromatin and markedly polylobated nuclear appearance [25, 28]. Larger cells with dispersed chromatin and small nucleoli may be admixed and predominate in some cases. Reed-Sternberg-like cells can be seen, simulating Hodgkin's disease [29]. In the smoldering form of ATLL, the cells may show minimal cytologic atypia and may even be diagnosed as small lymphocytic lymphoma in the WF. The larger cells usually show abundant cytoplasmic basophilia.

The neoplastic cells, regardless of cytologic subtype, are usually CD4+ T cells that strongly express the interleukin-2 receptor, CD25 [3]. High levels of soluble interleukin-2 receptors can also be found in the serum and can correlate with disease activity. CD7 is nearly always absent, but CD3 and other mature T-cell antigens are usually expressed.

**Intestinal T-cell lymphoma (+/- enteropathy) (EATL)**

WF: diffuse small cleaved, diffuse mixed small and large cell, diffuse large-cell immunoblastic.

Kiel: unclassified, pleomorphic medium and large cell, immunoblastic (HTLV-1 negative).

EATL was originally termed malignant histiocytosis of the intestine [30]. However, the demonstration of clonal T-cell gene rearrangement indicated that it was a T-cell lymphoma. The small bowel usually shows ulceration,
frequently with perforation. A mass may or may not be present. The infiltrate shows a varying cytologic composition with an admixture of small, medium, and larger atypical lymphoid cells. The adjacent small bowel may show villous atrophy associated with celiac disease [31]. The neoplastic cells are CD3+, CD7+ T cells, which also express the homing receptor CD103 (HML-1) [32]. The cells frequently express granzyme B, associated with cytotoxic T cells [33].

This disease occurs in adults, the majority of whom have a history of gluten-sensitive enteropathy. Patients usually present with abdominal symptoms such as pain, small bowel perforation, and associated peritonitis. The clinical course is aggressive.

Subcutaneous panniculitis-like T-cell lymphoma

WF: diffuse mixed small and large cell, large-cell immunoblastic, small cleaved cell.
Kiel: pleomorphic medium mixed and large cell (HTLV-1 negative).

Subcutaneous panniculitis-like T-cell lymphoma is sufficiently distinct to warrant separation from other forms of peripheral T-cell lymphoma [34]. The disease usually presents with subcutaneous nodules, primarily affecting the extremities. The nodules range in size from 0.5 cm to several centimeters in diameter. Larger nodules may become necrotic. In its early stages, the infiltrate may appear deceptively benign, and lesions are often misdiagnosed as panniculitis [34, 35]. However, histologic progression usually occurs, and subsequent biopsies show more pronounced cytologic atypia, permitting the diagnosis of malignant lymphoma.

As noted above, the cytologic composition of subcutaneous panniculitic T-cell lymphoma is extremely variable. The lesions may contain a predominance of small atypical lymphoid cells, often with clear cytoplasm, or larger atypical cells with hyperchromatic nuclei. Admixed reactive histiocytes are frequently present, particularly in areas of fat infiltration and destruction. The histiocytes are frequently vacuolated, owing to ingested lipid material. Vascular invasion may be seen in some cases, and necrosis and karyorrhexis are common.

Recent studies have further defined the immunophenotypic profile of this tumor, and have elucidated the nature of the 'necrosis' often seen in this neoplasm. The neoplastic cells uniformly express a CD8+ cytotoxic T-cell phenotype. In addition, the cells are positive for the cytotoxic associated proteins, perforin and TIA-1. These proteins mediate cytotoxicity and apoptosis by T cells and NK cells, and therefore may be responsible for the cellular destruction characteristic of these lesions. Further studies have confirmed that cellular destruction is apoptotic in nature, rather than necrotic. The neoplastic cells in six cases were strongly positive for bax and mcl-1, but negative for bcl-2. The apotag method also showed evidence of ongoing 'apoptosis' (see ref. [76] below).

A hemophagocytic syndrome is a frequent complication of subcutaneous panniculitic T-cell lymphoma [34]. Patients present with fever, pancytopenia, and hepatosplenomegaly. It is most readily diagnosed in bone marrow aspirate smears where histiocytes containing phagocytosed erythrocytes and occasionally platelets may be observed. The hemophagocytic syndrome usually precipitates a fulminant downhill clinical course. However, if therapy for the underlying lymphoma is instituted and is successful, the hemophagocytic syndrome may remit. A hemophagocytic syndrome is the cause of death in the majority of patients with subcutaneous panniculitic T-cell lymphoma. Dissemination to lymph nodes and other organs is uncommon and usually occurs late in the clinical course. The cause of the hemophagocytic syndrome appears related to cytokine production by the malignant cells. Both interferon gamma as well as granulocyte-monocyte colony-stimulating factor have been identified [35].

It is likely that subcutaneous panniculitic T-cell lymphoma is the process previously described as histiocytic cytophagic panniculitis. It had been thought that histiocytic cytophagic panniculitis was a malignant histiocytic proliferation. Although histiocytes may be numerous in these lesions, the malignant cells have a mature T-cell phenotype. Evidence for EBV has been absent.

γδ T-cell lymphoma

WF: diffuse small cleaved cell, unclassified.
Kiel: pleomorphic small cell, medium-sized cell (HTLV-1 negative).

The majority of peripheral T lymphocytes belong to the αβ subset, whereas only a minority are γδ T cells. Similarly, most peripheral T-cell lymphomas are of αβ T-cell derivation. However, there is a unique subtype of peripheral T-cell lymphoma that is derived from γδ T cells. γδ T-cell lymphoma presents with marked hepatosplenomegaly [36]. This tumor has also been referred to in the literature as hepatosplenic T-cell lymphoma. The homing pattern manifested by the malignant cells is similar to that of normal γδ T cells, which preferentially involve the sinusaloidal areas of the spleen and also the intestinal mucosa.

γδ T-cell lymphomas show a marked male predominance. Most patients are young adults [37]. The clinical presentation is that of marked hepatosplenomegaly in the absence of lymphadenopathy. Abnormal cells are usually present in the bone marrow but may be difficult to identify. They selectively infiltrate the bone marrow sinusoids and can be most easily recognized with immunohistochemical stains of bone marrow biopsy sections. A variant of γδ T-cell lymphoma with cutaneous disease has also been reported [35].

The cells of γδ T-cell lymphoma are usually moderate in size, with a rim of pale cytoplasm. The nuclear chromatin is loosely condensed with small inconspicuous nucleoli. Usually some irregularity of the nuclear contour can be seen. The liver and spleen show marked sinusaloidal
infiltration, with sparing of both portal triads and white pulp, respectively. The neoplastic cells have a phenotype that resembles that of normal γδ T cells. They are often negative for both CD4 and CD8, although CD8 may be expressed in some cases. Although they are positive for CD3, they are negative for antigens such as βF1, expressed on γδ cells, but positive for TCRδ. CD56 is also often positive [36, 37]. The neoplastic cells express markers associated with cytotoxic T cells, such as TIA-1. However, perforin is usually negative, suggesting that these cells are not functionally mature. In situ hybridization for EBV has been negative [37]. Isochromosome 7q appears to be a consistent cytogenetic abnormality [38].

Clinically, γδ T-cell lymphoma is aggressive [37]. Although patients may respond initially to chemotherapy, relapse has been seen in the vast majority of cases, and the median survival is less than three years. Rare long-term survival has been seen following autologous bone marrow transplantation.

Angiocentric (nasal and nasal-type) NK/T-cell lymphoma

**WF:** diffuse small cleaved, mixed small and large cell, large-cell immunoblastic.

**Kiel:** unclassified, pleomorphic small cell, medium and large cell (HTLV-I negative).

Angiocentric NK/T-cell lymphoma is a distinct clinicopathologic entity highly associated with EBV [39, 40]. The most common clinical presentation is with a destructive nasal or midline facial tumor. Palatal destruction, orbital swelling, and edema may be prominent [41]. Angiocentric lymphomas have been reported in other extranodal sites, including skin, soft tissue, testis, upper respiratory tract, and gastrointestinal tract. There are aggressive NK- and NK-like T-cell leukemias that have a similar phenotype and morphology, but are usually EBV negative [42-44].

Angiocentric NK/T-cell lymphoma is characterized by a broad cytologic spectrum. The atypical cells may be small or medium in size. Large atypical and hyperchromatic cells may be admixed, or may predominate. If the small cells are in the majority, the disease may be difficult to distinguish from an inflammatory or infectious process. In early stages there may also be a prominent admixture of inflammatory cells, further causing difficulty in diagnosis [45].

Because virtually all cases of nasal NK/T-cell lymphoma are positive for EBV, in situ hybridization studies with probes to EBV-encoded small nuclear RNA (EBER 1/2) may be very helpful in diagnosis and can detect even small numbers of neoplastic cells [46, 47]. Although the cells express some T-cell associated antigens, most commonly CD2, other T-cell markers, such as surface CD3, are usually absent [46]. Cytoplasmic CD3 can be found in paraffin sections. However, cytoplasmic CD3 can be found in NK cells, and is not specific for a T-cell lineage. In addition, molecular studies have not shown a clonal T-cell gene rearrangement, despite clonality being shown by other methods [46, 48, 49]. In favor of an NK-cell origin, the cells are nearly always CD56+; however, CD16 and CD57, other NK-cell antigens, are usually negative.

Angiocentric NK/T-cell lymphoma is much more common in Asians than in individuals of European background. Clusters of the disease have also been reported in Central and South America in individuals of Native American heritage [50]. Thus, a racial predisposition appears to play a role in the pathogenesis of angiocentric NK/T-cell lymphoma.

Nasal disease may be controlled with radiotherapy, but the relapse rate is high. Chemotherapy is generally used in conjunction with radiation therapy. The most common site of relapse is skin and subcutaneous tissue. A hemophagocytic syndrome is a common clinical complication, which adversely affects survival in angiocentric NK/T-cell lymphoma [51]. It is likely that EBV plays a role in the pathogenesis of the hemophagocytic syndrome.

Lymphomatoid granulomatosis (LYG) exhibits many similarities both clinically and pathologically to angiocentric NK/T-cell lymphoma [45]. Only recently it was considered to be part of the same disease spectrum, angiocentric immunoproliferative lesions (AIL). However, recent data indicate that LYG is an EBV-positive B-cell proliferation associated with an exuberant T-cell reaction [52]. LYG also presents in extranodal sites, but the most common site of involvement is the lung [53]. The kidney and central nervous system are also frequently involved as skin and subcutaneous tissue. The pattern in necrosis in both LYG and NK/T-cell lymphoma is very similar, emphasizing the likely importance of EBV in mediating the vascular damage.

Anaplastic large-cell lymphoma (ALCL)

**WF:** large cell, large cell immunoblastic.

**Kiel:** ALCL (Ki-1+ T cell).

**Classical ALCL.**

ALCL is characterized by pleomorphic cells that have a propensity to invade lymphoid sinuses [54]. Because of the sinusoidal location of the tumor cells, and their lobulated nuclear appearance, this disease was previously interpreted as a variant of malignant histiocytosis. Malignant histiocytosis as metastatic carcinoma or melanoma is also common.

A consistent feature is the expression of the CD30 antigen, which is a hallmark of this disease [55]. It has been referred to as Ki-1+ lymphoma [56]. However, antigen expression is not specific for ALCL, and is also seen in other forms of malignant lymphoma, including, of course, Hodgkin's disease [57].

ALCL can present in all age groups but is relatively more common in children and young adults. A high incidence of cutaneous disease has been reported [58]. A primary cutaneous form of ALCL is associated with
lymphomatoid papulosis, and differs clinically, immuno-
phenotypically, and at the molecular level [59–61]. Classical ALCL is associated with a characteristic chromo-
somal translocation, t(2;5) (p23;q35) [62, 63]. Recently, the genes involved in this translocation have been identified, and a polymerase chain reaction method has been developed to detect cells containing the fused NPM/ALK genes [64]. A polyclonal antibody to the p80 protein product of the fused genes also has been made, and it stains tumor cells containing the translocation [65].

The cells of classic ALCL have large, often lobated nuclei. Nucleoli are present but are usually not very prominent and frequently basophilic. In some cases, the nuclei may be round. The cytoplasm is usually abundant, amphophilic, with distinct cytoplasmic borders. A prominent Golgi region is usually apparent. Immunohistochemistry is very valuable in the correct diagnosis of ALCL. The prominent Golgi region usually shows intense staining for CD30 and epithelial membrane antigen (EMA) [66]. The cells usually exhibit an aberrant T-cell phenotype, frequently expressing CD2, CD4, and CD25. CD3 is frequently negative. We have recently identified a high incidence of expression of molecules associated with cytotoxic T-cells, such as perforin and TIA-1 (see ref. [77] below). This feature helps to distinguish ALCL from Hodgkin’s disease, which is usually negative for such markers.

Histologic variants of classic ALCL have been described. The histiocytic-rich variant contains a prominent admixture of histiocytes, which may lead to misdiagnosis as an inflammatory condition [67]. In this variant, the neoplastic cells are generally smaller and exhibit less pleomorphism than in classical ALCL. The histiocytic-rich variant is probably related to what has been termed the small-cell variant of ALCL [68]. In addition, there are more monomorphic variants, which may be difficult to distinguish from peripheral T-cell lymphomas, unspecific, composed of large lymphoid cells [61, 63, 69]. Again, staining with antibodies to CD30 can serve to highlight the malignant cells. Although the cells of PTL may be CD30+, staining is seldom as intense as in true ALCL.

Primary cutaneous ALCL

Primary cutaneous ALCL is a different disease and is closely related to lymphomatoid papulosis [70]. Indeed, lymphomatoid papulosis and cutaneous ALCL appear to represent a histologic and clinical continuum [60, 71]. Small lesions are likely to regress. Patients with large tumor masses may develop disseminated disease with lymph node involvement. However, primary cutaneous ALCL is a more indolent disease than other T-cell lymphomas of the skin [72]. Most patients with primary cutaneous ALCL have multiple skin lesions. Because the skin nodules may show spontaneous regression, usually a period of observation is warranted before the institution of any chemotherapy. Cutaneous ALCL is CD30+, but usually EMA negative. It also appears to lack the t(2;5) translocation [61].

ALCL Hodgkin’s-like (provisional) or ALCL-like Hodgkin’s disease

Hodgkin’s-related ALCL has been described as a provisional form of lymphoma that is difficult to distinguish from Hodgkin’s disease [73]. In many cases this process appears to be part of the spectrum of nodular-sclerosis Hodgkin’s disease (NSHD) [74]. It usually presents in young adults, often with a mediastinal mass. Skin lesions are not described. At low power, involved lymph nodes may show fibrous bands or capsular fibrosis resembling NSHD. An inflammatory background may be present focally, but elsewhere there is sheeting out of the malignant cells in a monomorphic fashion. In these monomorphic areas, the cells may lack the prominent eosinophilic nucleoli of Reed–Sternberg cells. Intrasinusoidal growth of the malignant cells may also be present.

It is still uncertain whether Hodgkin’s-like ALCL is part of the spectrum of Hodgkin’s disease or a variant of non-Hodgkin’s lymphoma [75]. It has been suggested that these patients respond poorly to conventional therapy for Hodgkin’s disease, but do respond to third-generation chemotherapy regimens used in the treatment of aggressive non-Hodgkin’s lymphoma [73].

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