Histopathology and Classification of T-Cell Lymphomas

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Introduction

T and NK cells derive from bone marrow precursor cells that undergo maturation in the central lymphoid organs (bone marrow and thymus) [1]. In the case of T-cells, maturation in the thymus includes T-cell receptor gene rearrangement, expression of T-cell receptor complex, and selection of αβ– or γδ-type T-cells [2–4]. These mature post-thymic T-cells reside in the peripheral lymphoid tissues, and lymphomas of these cells are considered peripheral T-cell lymphomas. NK cells mature in the bone marrow, do not require thymic "education," and circulate in the peripheral lymphoid organs [2–4]. The incidence of peripheral T-cell and NK-cell lymphomas varies across the world [5]. T/NK-cell neoplasms are more common in Asia and Latin America, probably a consequence of host genetic factors as well as environmental factors including infection with human T leukemia virus 1 (HTLV1), Epstein–Barr virus (EBV), and probably other viruses [6, 7]. In Northern Europe, enteropathy-associated T-cell lymphoma (EATCL) is common in Irish and Welsh populations, particularly those with certain HLA haplotypes [8, 9]. In the United States, the mature T/NK-cell neoplasms represent only 10–15% of non-Hodgkin lymphomas with an incidence of approximately 1.79/100,000 person-years [10].

The 2008 (World Health Organization [WHO]) classification of lymphomas applies clinical, morphologic, phenotypic, and molecular genetic features to define disease entities and provisional entities [1]. Some diseases are defined based on the presence of specific genetic abnormalities such as ALK+ anaplastic large cell lymphoma (ALCL), in which *anaplastic lymphoma kinase* (ALK) expression results for translocation of *ALK*. This is a major advance as prior classification systems relied primarily on histopathologic features alone. Within the mature T/NK cell neoplasms, there are 20 entities or provisional entities [5]. Figure 1.1 shows relative frequencies of the T-cell lymphomas other than primary cutaneous T-cell lymphomas. This list of lymphoma/leukemias of peripheral T or NK cells will likely change again as more is learned about the immunology and molecular genetics of these neoplasms.

Because of the heterogeneous composition of the lymphomatous infiltrate in many T/NK-cell lymphomas and the increased reliance on immunophenotypic and genetic features for the diagnosis and subclassification of T-cell lymphomas, procurement of adequate tissue, and proper handling of the fresh tissue is critical. Thus a few words on specimen processing are warranted. Communication among the hematologist, the

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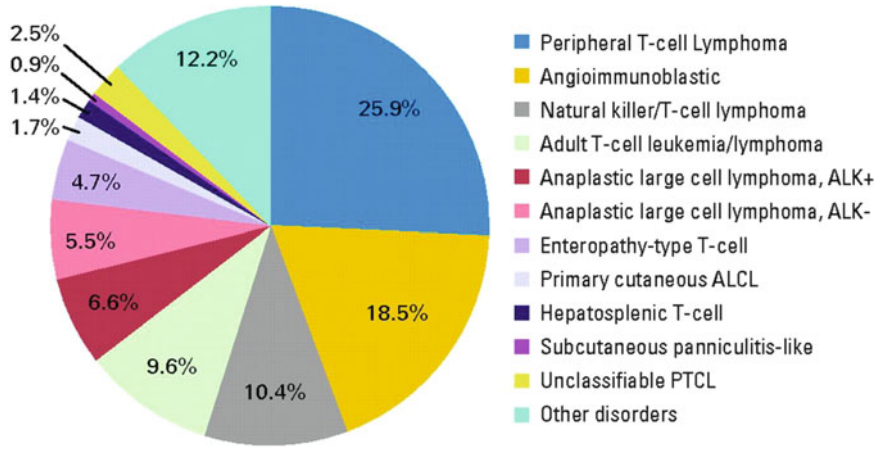

Fig. 1.1 Distribution of 1,314 cases by consensus diagnosis. Relative frequencies of mature T-cell lymphoma subtypes (except primary cutaneous types) in an adult patient population. Significant differences exist in different geographic regions (reprinted from International T-Cell Lymphoma Project [5], with permission from American Society of Clinical Oncology)

surgeon/procedure physician, and the pathologist is critical. In cases suspected of being lymphoma, an established "lymphoma protocol" should exist in which tissue is submitted in the fresh, sterile state to the pathology laboratory. This should be agreed upon by all parties so that clinicians and surgeons know that special handling is required and notify the laboratory at the time of procedure. Upon receipt of the fresh tissue, the pathologist can immediately evaluate the tissue by frozen section or touch imprints to assess specimen adequacy and to appropriately triage specimen for ancillary studies. If lymphoma is suspected, fresh tissue can be sent for cytogenetic studies, flow cytometry, and routine histopathology. Cultures can be sent if infection is suspected. The frozen tissue block can be retained at −20 °C or −70 °C for several days until it is decided whether further molecular genetic studies such as B- or T-cell receptor gene rearrangement studies are required. High-quality nucleic acids can be extracted from frozen tissues as opposed to fixed tissue and are the preferred source. The common practice of thawing the frozen block for permanent section "control" of the frozen is not indicated in lymphoma diagnosis since the morphology of that permanent section is substandard for fine morphologic/cytologic detail. After selecting tissue for these ancillary studies, the bulk of the remaining tissue can then undergo routine fixation and processing for histopathology studies.

With these introductory comments, we now focus on the pathologic features of the common peripheral T/NK-cell lymphomas and their differential diagnostic considerations.

Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL, NOS)

PTCL, NOS is the most common type of PTCL, representing approximately 25% of T-cell lymphomas [5, 11] (Fig. 1.1). Rare in children [12], PTCL, NOS is most often diagnosed in older adults [11]. While bone marrow, spleen, skin, and liver can be involved, the most common presentation is nodal [13]. B-Symptoms can accompany the lymphadenopathy, and extensive leukemic involvement is rare. PTCL, NOS has an aggressive clinical course, with a relative low (20–30%) 5 year failure-free survival [13–16].

The morphologic features are somewhat variable (probably a consequence of the fact that PTCL, NOS is not a homogeneous category). There is usually effacement of the normal lymph node architecture (Fig. 1.2a). Partial involvement may occur with the involvement of the paracortical region. A lymphoepithelioid pattern (so-called

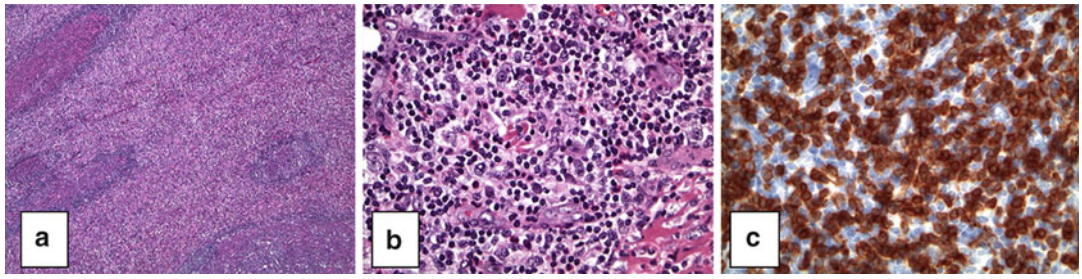

Fig. 1.2 Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). (**a**) HE ×40. An interfollicular infiltrate progressively replacing the follicles. (**b**) HE ×400. The abnormal infiltrate comprises atypical lymphocytes with abundant cytoplasm and irregular nuclei, histiocytes, eosinophils, and plasma cells. (**c**) CD3 ×400. The neoplastic cells are positive for CD3

Lennert lymphoma) can sometimes be seen in which the tumor is composed almost exclusively of small to intermediate neoplastic cells and histiocytes that form epithelioid granulomas [1]. Occasional reactive inflammatory cells such as histiocytes, plasma cells, and/or eosinophils are often seen (Fig. 1.2b). In addition, increased vascularity within the infiltrate is characteristic. The lymphoma cells may be monomorphous or quite polymorphous and pleomorphic. In most cases, the lymphoma cells are of intermediate size, have irregular nuclear borders, and have moderate amounts of pale cytoplasm. The presence of small or very large cells does not rule out this diagnosis. Nucleoli range from small and inconspicuous to very large. In some cases, large B-cells with reactive features (immunoblasts) or Reed–Sternberg-like cells can be identified. Rare cases can have follicular patterns similar to B-cell follicular lymphoma and are thought to be derived from follicular T-helper (T_{Fh}) cells [17, 18]. Whether this latter pattern represents a distinct entity is uncertain and awaits further investigation.

Immunophenotypic analysis shows most PTCL, NOS cells to be positive for CD3 (Fig. 1.2c) and CD4, but CD8-positive cases have also been described [19–21]. The cells are most often αβ T-cells and are thus positive for TCRβ (βF1). The most commonly lost "pan" T-cell markers are CD7 and CD5. When expressed, CD30 is detected with variable intensity, at levels significantly lower than those seen in ALCL. CD56 and cytotoxic markers such as granzyme B, perforin, and TIA-1 can be seen mainly in lesions positive for CD8 and are rare in cases positive for CD4. One to two percent of PTCL, NOS are positive for B-cell markers, mainly CD20, but this finding is not associated with positivity for Pax5. The cases with follicular pattern express follicular markers such as BCL-6, CD10, CXCL13, and PD1. The latter are markers expressed in T_{Fh}.

Gene expression profiling studies suggest a relationship with activated T-cells rather than with resting T-cells and suggest dysregulation of important cellular pathways such as proliferation, apoptosis, adhesion, and extracellular matrix remodeling [22]. No characteristic genetic abnormalities have been described in PTCL, NOS. However, gains of chromosomes 3, 5, 7q, 8q, 17q, and 22q have been described. Other abnormalities include loss of genetic material on chromosomes 1, 2, 3, 4q, 5q, 6q, 7, 8, 9p, 10q, 11, 12q, and 13q [23].

Angioimmunoblastic T-Cell Lymphoma

Approximately 15% of total T-cell lymphomas fall into this category [5]. Most patients are adults and present with generalized lymphadenopathy, high-stage disease, and B-symptoms. Involvement of extranodal sites such as skin, liver, spleen, and bone marrow is common [24–26]. Patients appear to have evidence of immune system dysfunction, including recurrent infections, cold agglutinins, polyclonal hypergammaglobulinemia, autoimmune hemolytic anemia, and rheumatoid factor [27]. The immune deficiencies associated with

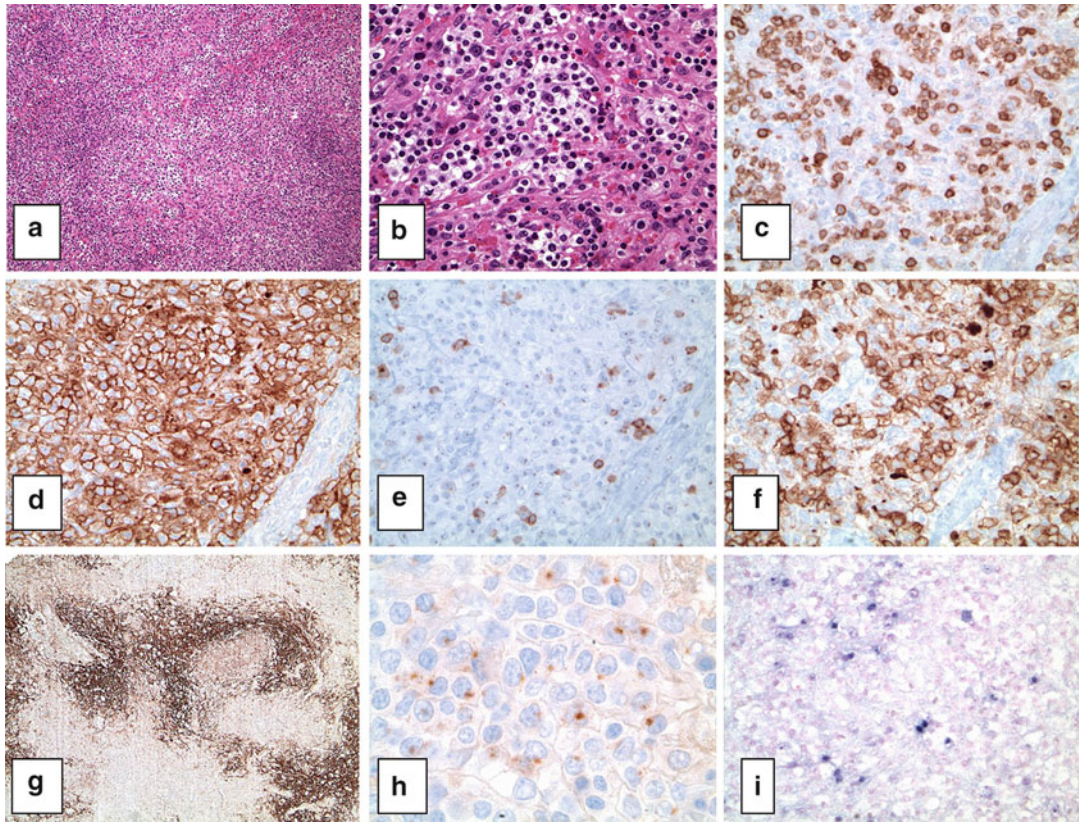

Fig. 1.3 Angioimmunoblastic T-cell lymphoma. (**a**) HE ×100 sheets of intermediate-sized cells completely efface the lymph node architecture. Vascular proliferation noticeable in the background. (**b**) HE ×400. Same features as in (**a**), with a better illustration of the retraction artifact, a consequence of the abundant cytoplasm. (**c**) CD3 ×400. (**d**) CD4 ×400. (**e**) CD7 ×100 (**f**) CD10 ×400. (**g**) CD21 ×100. (**h**) CXCL13 ×400. (**i**) EBER ×100

angioimmunoblastic T-cell lymphoma (AITL) are at least partially responsible for the poor prognosis of AITL (median survival less than 3 years). In up to 25% of cases of AITL, aggressive B-cell lymphomas can develop, further complicating the clinical course of this neoplasm [28].

Histologically, the lymph node is diffusely replaced by a neoplastic infiltrate (Fig. 1.3a). Germinal centers are usually absent or, if present, demonstrate regressive transformation. Presence of germinal centers does not preclude the possibility of AITL, since some cases of early involvement may show this feature. The subcapsular sinuses are usually spared or enlarged, even as the neoplastic infiltrate extends into the pericapsular fibroadipose tissue. Numerous proliferating vessels corresponding to high endothelial venules may form an arborizing vascular network (Fig. 1.3b). The infiltrate is polymorphous, a feature that while characteristic may cause diagnostic difficulty since many of the cells are reactive inflammatory cells such as eosinophils, histiocytes, small lymphocytes, and plasma cells. The neoplastic cells are usually intermediate-sized cells, with abundant cytoplasm, often leading to a "clear cell" or "fried egg" appearance (Fig. 1.3b). Atypia may be mild. The spacing of cells may impart a relatively depleted look at low magnification. Rare large immunoblasts are usually present and Reed–Sternberg-like cells may be seen. While difficult to observe on hematoxylin and eosin stains, follicular dendritic cells proliferate and form distorted networks, usually in paracortical and perivascular areas (Fig. 1.3g).

The immunophenotype of AITL indicates that the cell of origin of this lesion is the CD4-positive

follicular T-helper cell [24–26, 29]. The lymphoma cells are positive for CD2, CD3 (Fig. 1.3c), CD4 (Fig. 1.3d), CD5, CD7, CD45, and βF1. Characteristically, they are also positive for T_{FH} markers such as CD10 (Fig. 1.3f), CXCL13 (Fig. 1.3h), PD1, and ICOS [30]. The immunoblasts are positive for EBV in most cases (Fig. 1.3i). The proliferating follicular dendritic cells are positive for CD21, CD23, and CD35, markers that also highlight the abnormal architecture of these proliferations. Occasionally, the lymphoma cells show abnormal loss of T-cell markers (Fig. 1.3f).

The large B-cell component may progress to sheets of monoclonal cells, warranting a diagnosis of EBV+ DLBL that may obscure the underlying AITL [31]. In some cases, a treated AITL may relapse as EBV+ DLBL.

While the above features make AITL recognizable in a lymph node, specific morphologic features may be lacking when involving an extranodal site such as skin or bone marrow. A high index of suspicion is required so that appropriate studies can be performed to confirm lymphomatous involvement.

Molecular genetic testing for T- and B-cell receptor gene rearrangements shows a T-cell clone in >95% of cases. A B-cell clone (EBV-driven) can be detected in half of the cases [32, 33]. Gene expression profiles performed in cases of AITL show similarity between T_{Fh} and AITL cells [34]. Conventional cytogenetic analysis usually does not lead to the identification of characteristic abnormalities. The most often encountered abnormalities are trisomies of chromosomes 3, 5, and X [24].

Anaplastic Large Cell Lymphoma, ALK-Positive

By definition, the neoplasms in this category are positive for translocations involving the *ALK* located at 2p23 [1]. Most patients are young, in the first three decades of life (mean age 21.3 years) [35, 36], with a slight male predominance. Approximately two-thirds of patients present with advanced-stage disease and B-symptoms [36]. Forty-six percent of patients have extranodal involvement with bone, bone marrow, spleen, and subcutaneous tissue being the most common sites. The prognosis of ALK+ ALCL is favorable, as the 5 year survival approaches 80%. Interestingly, patients with different translocations involving *ALK* have similar survival [37]. The adult or older patients with ALCL seem to have a worse prognosis than pediatric patients.

Histologic sections can show one of several morphologic variants. In all the variants, the distribution of the neoplastic cells is predominantly intra-sinusoidal, with the neoplastic cells forming sheets [36, 38]. Perivascular cuffs of malignant cells can be seen in some cases (Fig. 1.4b). In more advanced cases, the lymph node is completely effaced. The neoplastic cells in the common, classical variant (over 60% of cases) are large, with abundant cytoplasm and one or multiple nuclei (Fig. 1.4a). The nuclei are abnormally lobated, often with conspicuous eosinophilic nucleoli. Cells with indented or comma-shaped nuclei and abundant cytoplasm (so-called "hallmark cells") are characteristically seen. In addition to the common type, there are several other morphologic variants: lymphohistiocytic, small cell, Hodgkin-like, sarcomatoid, and giant cell rich. Some cases may demonstrate more than one variant and, upon relapse, transformation to another variant morphology may occur [35].

The immunophenotype of this entity is characterized by strong positivity for CD30 in most large cells, with a membrane and Golgi pattern, similar to that observed in Reed–Sternberg cells [1, 39] (Fig. 1.4b). Many of the T-lineage markers are lost, making lineage determination difficult. The stain for CD3 is negative in many cases (Fig. 1.4d), but expression of CD2, CD4, or CD5 can be preserved. EMA and CD43 can be detected in most cases [35, 40]. A finding limited to ALCL is the concurrent expression of CD4 and of cytotoxic markers such as granzyme B, TIA-1, and perforin [41, 42]. Similar to Reed–Sternberg cells, the neoplastic cells in ALCL can be negative for CD45 (LCA). Clusterin reactivity in a dot-like Golgi pattern may be helpful in identifying cases of ALCL [43]. By definition, ALK expression can be demonstrated (Fig. 1.4c).

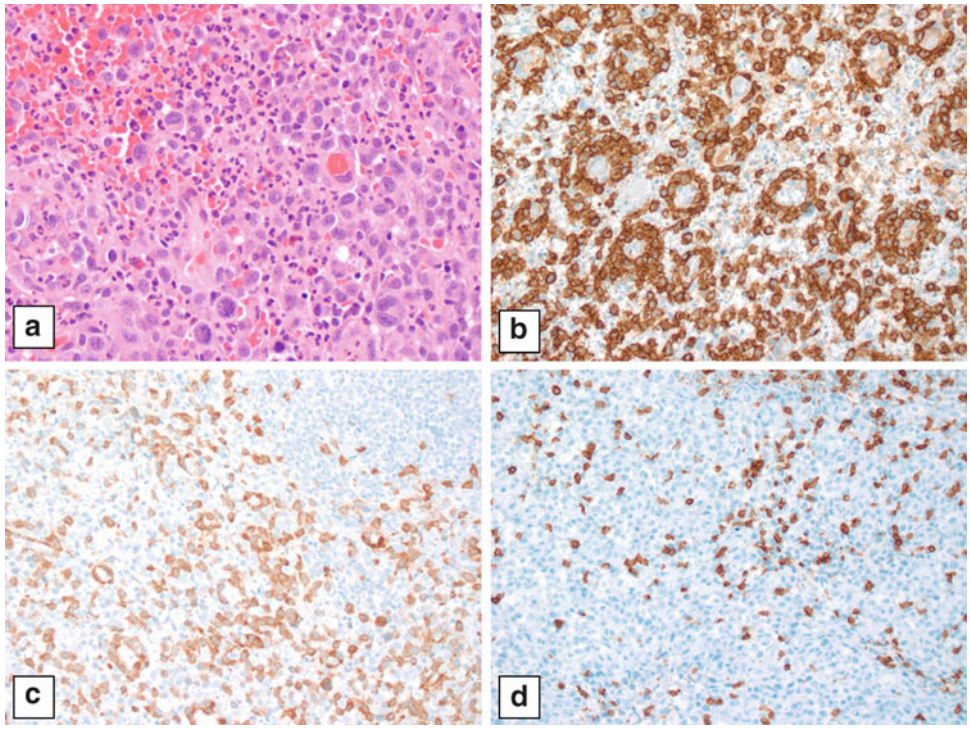

Fig. 1.4 Anaplastic large T-cell lymphoma, ALK positive. (**a**) HE ×400. Sheets of large cells, with one or multiple nuclei with conspicuous nucleoli. (**b**) CD30 ×200. (**c**) ALK1 ×200. Cytoplasmic and nuclear patterns. (**d**) CD3 ×200

The karyotype of ALCL, ALK+ is characterized by translocations involving *ALK*. The consequence of these translocations is abnormal expression of ALK, a protein normally present on the membrane of embryonic and central nervous system cells. Most cases of ALCL, ALK positive harbor the t(2;5)(p23;q35) translocation (*NPM1-ALK*) [44, 45]. The second most common translocation is t(1;2)(q25;p23) (*TPM3-ALK*), the rest of the cases having one of the other abnormalities: Inv(2)(p23q35) (*ATIC-ALK*), t(2;3)(p23;q12) (*TFG-ALK*), t(2;17)(p23;q23) (*CLTC-ALK*), t(X;2)(q11-12;p23)(*MSN-ALK*), t(2;19)(p23;p13.1) (*TPM4-ALK*), t(2;22)(p23;q11.2) (*MYH9-ALK*), t(2;17)(p23;q25) *(ALO17-ALK)* [44, 45]. Additional genetic abnormalities can be identified in ALCL, but their clinical significance is unclear. The intracellular distribution of ALK is determined by the partner of translocation. In the cases with *NPM-ALK* fusion (the majority of ALCL), the staining pattern is cytoplasmic and nuclear (NPM shuttles between the nucleus and the cytoplasm). Cytoplasmic staining with perinuclear intensification characterizes cases with *TPM3-ALK*. Diffuse cytoplasmic staining can be seen in cases with translocations involving *ATIC, TFG, TPM4, MYH9, ALO17*. Exclusive membrane positivity is seen in cases with *MSN*. Granular cytoplasmic stain is the consequence of *CLTC-ALK* translocation.

Most cases of ALCL, ALK+ have clonal rearrangements of the *TCR* gamma locus.

ALCL, ALK negative is a provisional category in the current WHO classification [1]. Unlike the ALK-positive cases, ALCL, ALK-negative patients are older adults (median age 58 years), with a similar slight male preponderance [46]. The prognosis of patients with ALCL, ALK negative is significantly worse than that of patients with ALCL, ALK positive and may be superior to patients with PTCL NOS [36]. The sites of involvement are similar to those for ALK positive ALCL. The diagnosis of cases with primary exclusive skin involvement is difficult, as

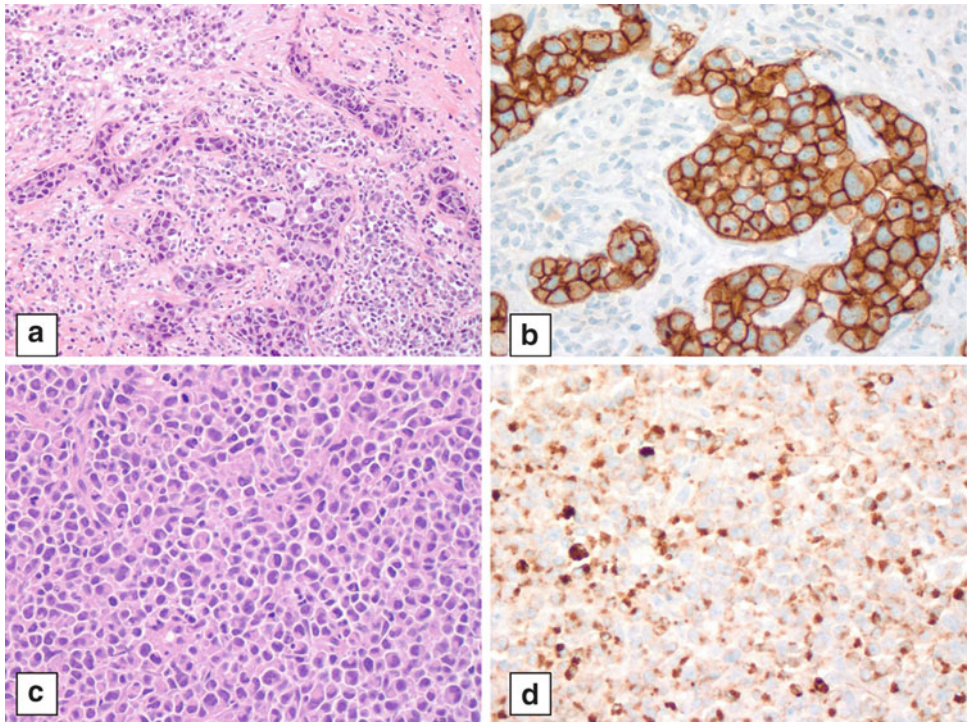

Fig. 1.5 Anaplastic large T-cell lymphoma, ALK negative. (**a**) HE ×200. Large atypical cells with intra-sinusoidal pattern. (**b**) CD30 ×400. (**c**) HE ×400. (**d**) Clusterin ×400. Paranuclear dots

the morphology of these lesions does not allow their differentiation from other CD30-positive primary cutaneous T-cell lymphoproliferative disorders. The histologic characteristics of ALCL, ALK negative are similar to those of ALCL, ALK positive, the common variant, with the exception of negativity for ALK (Fig. 1.5a–d). In cases with a morphology deviating from that of classical ALCL, the diagnosis of PTCL, NOS is preferred. Obviously, no translocations involving ALK can be identified by conventional cytogenetics in ALCL, ALK negative.

Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a lymphoproliferative disorder associated with HTLV-I infection [1]. This retrovirus is endemic in specific geographic areas such as Southwestern Japan, the Caribbean basin, South American, and Africa. The oncogenic mechanism through which HTLV-1 induces neoplasia is not completely elucidated, but studies suggest that the viral Tax and HBZ gene products are important in the pathogenesis of ATLL [47–49]. It is increasingly clear that genetic and epigenetic changes in host cells are important in transformation and development of this disease [50]. The prognosis of patients with ATLL depends on the form of ATLL (see below), serum calcium, and lactate dehydrogenase [51, 52]. The patients with chronic and smoldering forms have a protracted course, while acute forms result rapidly in death. Suppression of the immune system of ATLL patients can result in lethal infections.

The clinical presentation of ATLL is variable, as there are acute forms, lymphomatous, chronic, and smoldering cases of ATLL [53, 54]. Bone marrow, lymph node, and skin involvement are common. In the acute presentation, there are increased white blood cell counts (with malignant

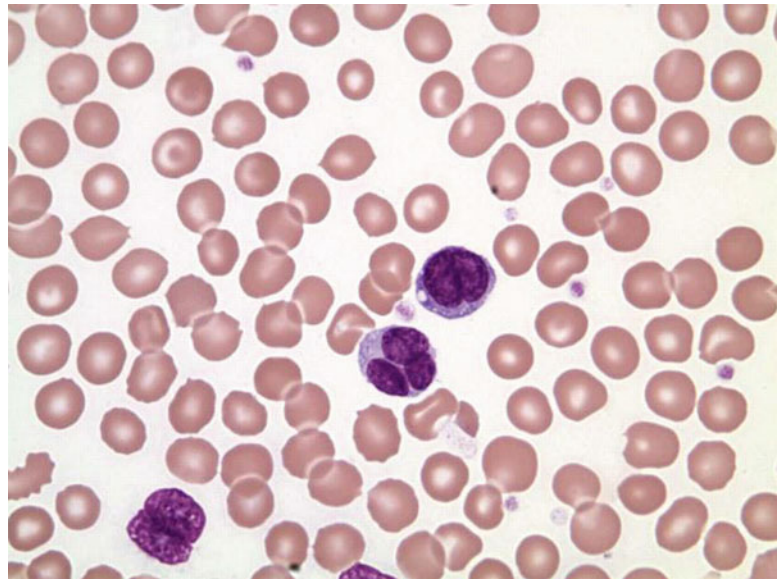

Fig. 1.6 Adult T-cell leukemia/lymphoma. Peripheral blood, ×1,000. Atypical lymphocyte ("flower cell")

cells) and extensive bone marrow involvement. Hypercalcemia can be secondary to bone destruction. Hepatosplenomegaly systemic symptoms and infections are frequent. In the smoldering presentation, the WBC is not significantly increased and malignant cells are less than 5% of the circulating cells. Bone marrow involvement is limited (and there is no hypercalcemia). In lymphomatous cases, there are widespread enlarged lymph nodes, variable blood involvement, and elevated lactate dehydrogenase. Infections are a consequence of immunodeficiencies. In the chronic form, the most common presentation is with a skin rash, which can slowly progress. The acute form can be present at diagnosis, but in a significant number of cases, they arise in patients with the chronic or smoldering forms of ATLL [54].

The morphology of the neoplastic cells is variable, from small to large. Most cells in leukemic cases are of intermediate size, with moderate cytoplasm and irregular nuclei ("flower cells") (Fig. 1.6). The patterns of tissue involvement are also variable, from diffuse sheets of intermediate cells, to patterns reminiscent of AITL or ALCL. Large, Hodgkin-like cells that are positive for EBV are further indication of the immunosuppressed status of the patient. In the skin, the neoplastic cells can form infiltrates similar to MF in tumor or plaque stages.

As the cell of origin is the CD4-positive T-helper cells, the immunophenotype of ATLL is positive for CD2, CD3, CD4, and CD5. CD7 is usually lost, but there is strong positivity for CD25 [55]. Also expressed are CCR4 and FOXP3 [56]. Large, anaplastic cells can be positive for CD30. However, this does not warrant a diagnosis of ALCL.

There are no specific cytogenetic abnormalities in ATLL, but molecular tests can identify clonal rearrangements of the *TCR* genes. Integration of HTLV-I in the host genome differentiates patients with ATLL from healthy carriers [47, 48, 55].

In addition to tests designed to characterize the tumor cells, immunologic and molecular tests designed to identify exposure and infection with HTLV-I should always be integrated in the workup of cases of ATLL.

Extranodal NK/T-Cell Lymphoma, Nasal Type (ENKTL)

This is a neoplasm of cytotoxic cells (NK cell most often) characterized by vascular damage, necrosis, and tissue destruction, usually associated

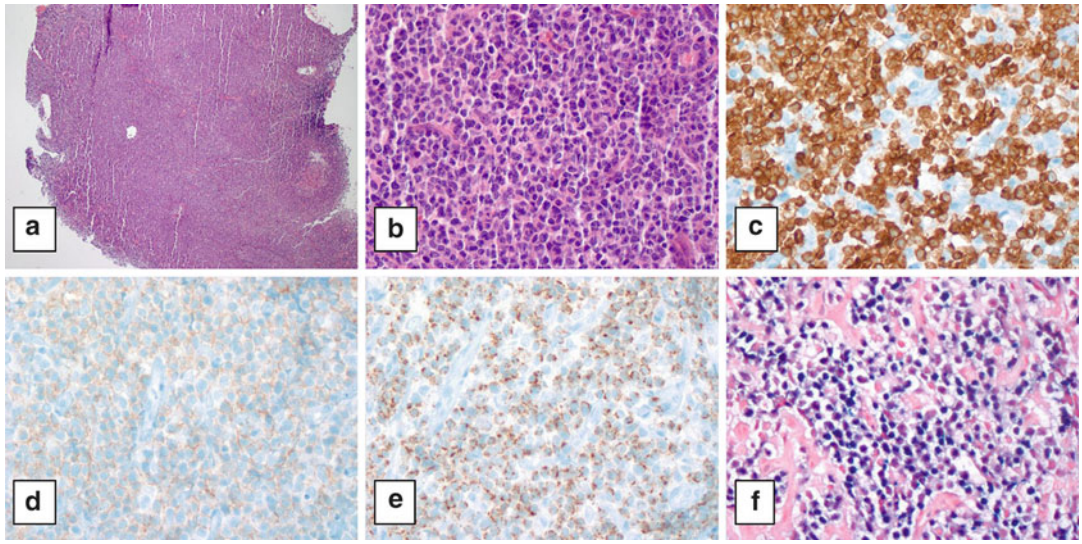

Fig. 1.7 Extranodal NK/T-cell lymphoma, nasal type. (**a**) HE ×20. Focal areas of necrosis. (**b**) HE ×400. Pleomorphic cells with diffuse pattern, with dense chromatin. (**c**) CD3 ×400. The stain for CD3 is positive, as the epitope is detected in the cytoplasm (the cells are negative for surface CD3). (**d**) CD56 ×400. The lymphoma cells are positive for CD56. (**e**) TIA-1 ×400. (**f**) EBER ×400

with EBV [1]. This association suggests that EBV plays an important etiologic role in pathogenesis of this lymphoma.

The increased prevalence of this neoplasm in Asians and Native Americans also points to a component of genetic susceptibility of these populations to this type of neoplasms [57]. Most patients are adult males and cases arising in post-transplant patients have been described. There is involvement of the nasal cavity or other areas of the upper aerodigestive tract. Local extension and destruction of midline facial structures occur, explaining the prior descriptive term for this lymphoma—lethal midline granuloma. Involvement of extranasal sites may also occur as the primary site of disease such as skin, testis, soft tissue, and gastrointestinal tract. Advanced-stage disease may involve bone marrow, and hemophagocytosis may be present. Historically ENKTL was thought to have a poor prognosis [58, 59]. However, due to advances in therapy, the outcome of ENKTL is now variable as a significant subset of patients responds to radiation and chemotherapy [60, 61]. Extranasal presentation is thought to be a poor prognosis feature [62].

Most times, the symptoms at presentation are the result of extensive tissue destruction by neoplastic infiltrate that involve the vasculature. This imparts an angiocentric and angiodestructive pattern. Fibrinoid necrosis may be seen even without neoplastic infiltrate. As a consequence, necrosis is a constant feature (Fig. 1.7a). The cells can infiltrate and fill the nasal cavities or can form tumor nodules at the involved locations. The malignant cells can be small, without conspicuous morphologic abnormalities, intermediate-sized, with irregular nuclear contour and fine or blastoid chromatin, or large, with vesicular chromatin (Fig. 1.7b). Most cases have intermediate-sized cells, and in all cases, a prominent inflammatory infiltrate can be associated with the neoplastic cells, probably a consequence of the necrosis. The cell size has been thought to have prognostic value with small cell cases being thought to have a better prognosis than large cell ones. Blood and bone marrow involvement can occur. On imprints or blood/bone marrow Wright–Giemsa smears, the cells have open chromatin and moderate amounts of cytoplasm with azurophilic granules.

The immunophenotype is that of cytotoxic cells, most often NK cells (positive for CD2, CD56, granzyme B, perforin, and TIA-1 and negative for surface CD3, CD4, CD5, and βF1) [59] (Fig. 1.7c–e). The great majority (if not all) of cases are positive for EBV (Fig. 1.7f). Most tumor cells should be EBV+ [58].

Molecular studies in most cases show no evidence of clonal rearrangement of the TCR receptor genes. The presence of rare cases positive for TCR δ clonal rearrangements has suggested that probably not all these neoplasms are of NK lineage, justifying their naming as NK/T-cell tumors [63]. While not pathognomonic for this entity, abnormalities of chromosome 6 (del(6)(q21q26) and i(6)(p10)) are relatively common. Other cytogenetic abnormalities that can be seen involve the chromosomes 1, 2, 4, 5, 6, 7, 11, and 15 [64, 65].

Aggressive NK-cell leukemia is a neoplasm with leukemic presentation and accelerated, fatal clinical course [1]. The association with EBV, the similar immunophenotype of the malignant cells, as well as the higher incidence in Asians has led to the hypothesis that it may represent the leukemic counterpart of the extranodal NK/T-cell lymphoma, nasal type. However, this idea is not yet fully accepted, as the patients with aggressive NK-cell leukemia tend to be younger than those with ENKTL, the skin is spared, and some genetic abnormalities seem to have preferential association with only one of the two entities [1, 66, 67]. As these cases are relatively rare, the existing data are probably not sufficient for a definitive conclusion.

EBV-Positive T-Cell Lymphoproliferative Disorders of Childhood (EBVTCLD)

EBVTCLD are composed of two main entities [1]: Hydroa vacciniforme-like lymphoma and systemic EBV-positive T-cell lymphoproliferative disease of childhood. This latter entity is rare and is characterized by the proliferation of EBV-infected T-cells with a cytotoxic phenotype. It progresses rapidly usually leading to death. Many of its features overlap with those of aggressive NK-cell leukemia [68–70]. This systemic disease arises in two types of circumstances [71]: shortly after an acute EBV [69, 70, 72] infection and in chronic active EBV infection (CAEBV) [68]. In the former setting, the process has been described to be associated with fulminant hemophagocytic syndrome. The cases of CAEBV that previously have been associated with clonal T-cell populations now are understood to be part of the spectrum of manifestation of the EBV-positive T-cell lymphoproliferative disorders of childhood.

The clinical presentation of EBVTCLD is acute, with fever and constitutional symptoms. The patients develop hepatosplenomegaly and pancytopenia. The EBV titers are high and EBV viral DNA is present in blood. The patients rapidly progresses with the development of coagulopathy, multisystem organ failure, sepsis, and hemophagocytic syndrome.

Morphologically, the pattern of involvement is not characteristic, as malignant cells with no definitive cytologic abnormalities infiltrate organs without forming tumors. Most malignant cells are present in the sinuses of lymph nodes, bone marrow, spleen, liver. Immunophenotyping may be required to see the extent of the lymphomatous infiltrate.

The immunophenotype of the cells is positive for CD2, CD3, TIA-1, and EBV. Cases evolving from CAEBV are positive for CD4 [71, 73], while cases from fulminant mononucleosis are positive for CD8 [72].

There are no pathognomonic conventional cytogenetic abnormalities associated with EBVTCLD, but the tests for *TCR* genes can identify clonal rearrangements.

Hydroa vacciniforme-like lymphoma is a cutaneous T- or NK-cell neoplasm primarily identified in the skin of children from Asia, and South and Central America. It can be precipitated by events such as sun or mosquito bite sensitivity (also, it involves the sun-exposed skin) [74–76].

Morphologically, the lesions are papulovesicular eruptions that progress to ulceration and scarring, becoming associated with lymphadenopathy and hepatosplenomegaly. The neoplastic cells involve all the skin layers and display

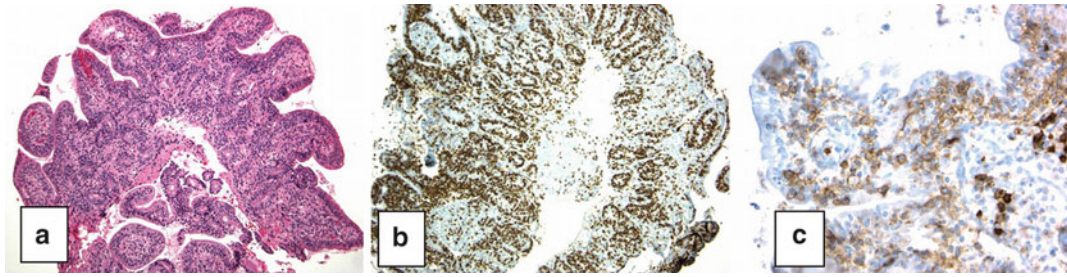

Fig. 1.8 Enteropathy-associated T-cell lymphoma. (**a**) HE ×100. Atypical infiltrate in the lamina propria, invading the crypts. The overall architecture is abnormal, with effacement of the villi. (**b**) CD3 ×100. The cells in the lamina propria and in the surface mucosa are positive. (**c**) CD8 ×400. The lymphoma cells are positive

angiocentricity, leading to necrosis. They are usually small, without overt cytologic atypia.

The immunophenotype is that of cytotoxic T-cells (positive for CD2, CD3, CD5, CD8) or that of NK cells (positive for CD2, CD56) and in most cases are positive for EBV.

The molecular tests show positivity for *TCR* rearrangement of tumors composed of T-cells and negativity for the tumors of NK cells.

Enteropathy-Associated T-Cell Lymphoma (EATCL)

EATCL is a neoplasm thought to be derived from intra-epithelial T-cells. It is most prevalent in areas with high incidence of celiac disease (Northern Europe) [9]. Patients that have EATCL associated with celiac disease usually are positive for HLA DQ2 or DQ8, pointing to host genetic factors being involved in this lymphoma [77]. Patients present with abdominal pain. Many patients do not have a preexisting diagnosis of celiac disease. Patients with established celiac disease may develop EATCL. Such patients may have refractory celiac disease and present with loss of response to therapy and intestinal perforation. Most patients have a poor prognosis and death is often the result of intestinal complications (perforation, obstruction, malabsorption).

Morphologically, the lymphoma forms intestinal masses with superficial mucosal ulceration. The pattern of the neoplastic infiltrate is usually diffuse. A key histologic feature is invasion of the surface and crypt epithelium. The presence of the neoplastic infiltrate is associated with villous atrophy and/or crypt hyperplasia (features of celiac disease) (Fig. 1.8a). When the specimen is small, or the biopsy is obtained at the edge of the lesion, the tumor infiltrate may be sparse, and abnormalities of the mucosal architecture and the lymphoid infiltrate in the epithelium and lamina propria may suggest the correct diagnosis [78]. The morphology of the tumor cells is variable and is the basis for the classification of EATCL in two subcategories. In classical EATCL (type 1), the tumor cells are relatively polymorphous, medium-sized, with irregular nuclei with vesicular chromatin and small nucleoli. There is significant inter-case variability in the morphology of the neoplastic cells, some cases may be quite pleomorphic, having the cytologic appearance suggestive of ALCL. In type II EATCL, the neoplastic cells are relatively monomorphic, small to intermediate sized, with clumped chromatin and pale cytoplasm. This latter type of EATCL is rarer (10–20% of cells) and often is not associated with a history (or evidence) of celiac disease.

The immunophenotype of the two types of EATCL is that of cytotoxic T-cells. They typically express CD3 (Fig. 1.8b), CD7, CD103, and βF1 but are negative for CD5, CD4, CD8, and CD56. Uncommonly, cases may be CD8+. Cases of type II EATCL differ in their phenotype and are more commonly CD8+/CD56+ [78] (Fig. 1.8c). In many cases, a subset of the tumor cells is positive for CD30. EBV is negative.

Molecular tests show that the *TCR* genes are clonally rearranged in both types of EATCL. The association with HLA DR2 or DR8 is stronger

for classical EATCL. Both types of EATCL are positive for segmental amplification of 9q31.3-qter or for deletions in 16q12.1 [8]. The classical form can also show gains of 1q and 5q, while amplifications of MYC (8q24) can be seen in the type II (monomorphic) variant.

Hepatosplenic T-Cell Lymphoma (HSTCL)

This is a rare type of lymphoma, mostly diagnosed in young or middle-aged males with a median age of 38 years in a recent series [79]. Most cases are γδ-T-cell lymphomas, although αβ-T-cell types are reported in 20% of cases [80–83]. The lymphoma involves the liver, spleen, and the bone marrow with an intra-sinusoidal pattern. A significant fraction of these lymphomas arise in the context of immunosuppression, often in the post-transplant setting or in the context of inflammatory bowel disease patients treated with immunomodulatory therapy (thiopurines and TNF-α inhibitors) [83, 84]. Patients present with hepatosplenomegaly, altered liver functions, and often with marked thrombocytopenia. It is an aggressive lymphoma with median overall survival of less than 1 year [79, 85].

The morphologic findings consist of an abundant, intra-sinusoidal infiltrate in the liver, spleen, and bone marrow (Fig. 1.9a). This infiltrate is composed of small to intermediate cells with moderate to abundant pale cytoplasm and nuclei without major atypical features.

The immunophenotype is that of γδ T-cells or, less commonly, αβ T-cells. They express CD3 (Fig. 1.9b), TCRδ (if γδ T-cell type), TIA1 (Fig. 1.9c), and granzyme M. These cells are negative for CD7 and for granzyme B or perforin. As on NK cells, the killer inhibitor receptors (KIRs) are expressed, but the cells can be negative for CD94 [83].

Molecular studies have shown that these tumors have clonal rearrangements of the *TCR* γ genes. Only the αβ cases have clones with rearranged *TCR* β genes. Most cases of HSTCL harbor abnormalities of chromosome 7: isochromosome 7q or ring chromosome 7. Other abnormalities may include trisomy 8 and loss of sex chromosomes [83].

Subcutaneous Panniculitis-Like T-Cell Lymphoma

This is a rare type of lymphoma preferentially involving the subcutaneous fibroadipose tissue. The cell of origin is thought to be the mature cytotoxic αβ T-cell [1, 86, 87].

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is slightly more common in females than in males, and in early stages, it may show features similar to those of lupus profundus panniculitis (some patients may have a history of systemic lupus erythematosus) [87]. The lesions are most often located on the trunk or on the extremities and can range from small to several centimeters in diameters. The infiltrate lacks epidermotropism, and ulceration is relatively rare. Unlike γδ T-cell lymphomas, SPTCL has a good prognosis (5 year survival of 80%) [88]. In SPTCL cases with poor prognosis,

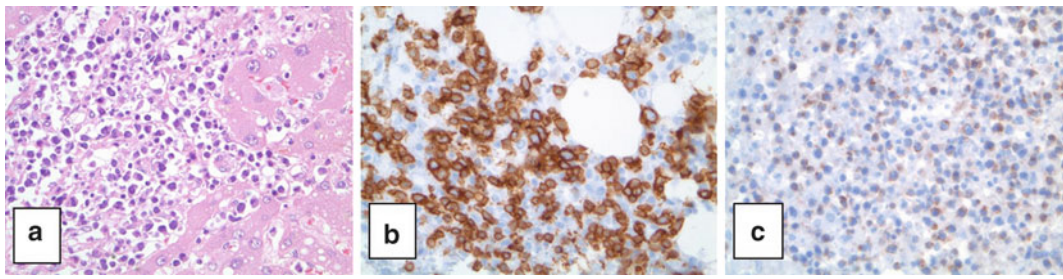

Fig. 1.9 Hepatosplenic T-cell lymphoma. (**a**) HE ×200. Intra-sinusoidal infiltrate. (**b**) CD3 ×200. (**c**) TIA-1 ×200

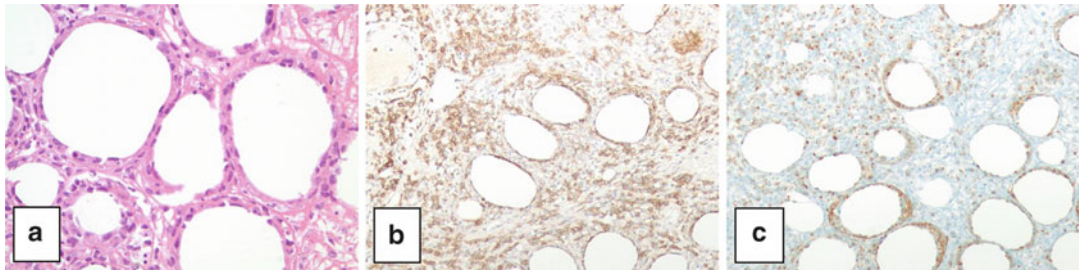

Fig. 1.10 Subcutaneous panniculitis-like T-cell lymphoma. (**a**) HE ×400. Rimming of the adipocytes. (**b**) CD8 ×200. (**c**) Granzyme B ×200

hemophagocytic syndrome has been described as a constant feature [87].

Morphologically, the tumor infiltrate involves the subcutaneous fat lobules and spares the septa. The neoplastic cells are small, with nuclear atypia, and they completely surround or "rim" the adipocytes (Fig. 1.10a). This latter feature is characteristic, albeit not specific [89]. Fat necrosis and increased histiocytes are constant features of most tumors.

The immunophenotype is that of mature cytotoxic αβ T-cells, with random losses of normal surface markers. As such, the cells express T-cell markers such as CD2 and CD3, TCRβ, and are usually CD8+/CD4− (Fig. 1.10b). Cytotoxic molecules are expressed such as granzyme B (Fig. 1.10c), TIA1, and perforin. CD56 is not expressed. Molecular findings confirm the clonal rearrangement of *TCR* γ or β.

Mycosis Fungoides (MFs)

MF is the most common type of cutaneous T-cell lymphoma, with approximately 1,000 new cases diagnosed in the United States each year [11]. The cell of origin is the mature CD4-positive T-cell with propensity for homing in the skin [1]. The median age at diagnosis is 55 years, with a male predominance. It is twice as common in African Americans than in Caucasians [90]. It has an indolent clinical course with slow progression, oftentimes spanning a decade or more [90]. Diagnosis may be delayed due to the indolent course and subtle manifestations. Patients present with erythematous patches with fine scale in non-sun exposed areas and can progress to thickened plaques, and finally to tumors [91]. The prognosis of patients with MF is dependent on the extent of skin involvement and on the clinical stage. Patients with limited skin involvement have an excellent prognosis, while the patients with tumors or increased large cells have a more aggressive course, requiring systemic chemotherapy [91]. Lymph node or leukemic dissemination may occur and portend a poor prognosis. Modern clinical staging systems such as the ISLC/EORTC proposal make use of clinical and pathologic features to stratify patients. The pathologic features now have specific criteria for blood and lymph node involvement. The former requires morphologic, flow cytometric, and molecular genetic assessment of the blood [92].

Clinical variants have been recognized. Folliculotropic MF involves the head and neck and manifests as small folliculotropic papules, sometimes with alopecia [93, 94]. Pagetoid reticulosis is a localized lesion, usually involving the extremities. It may become a solitary plaque that remains localized [95]. Granulomatous slack skin presents with pendulous folds of lax skin involving intertriginous areas [96, 97].

The neoplastic infiltrate of MF can form patches, plaques, or tumors (in order of the progression). At early stages (patch), the malignant cells display remarkable epidermotropism [98] (Fig. 1.11). In the epidermis, most lymphoma cells are seen in the basal layer and are usually surrounded by areas of clearing or halos. Neoplastic cells may cluster within the epidermis to form Pautrier microabscesses (Fig. 1.11b). In the superficial dermis, the infiltrate is mainly in

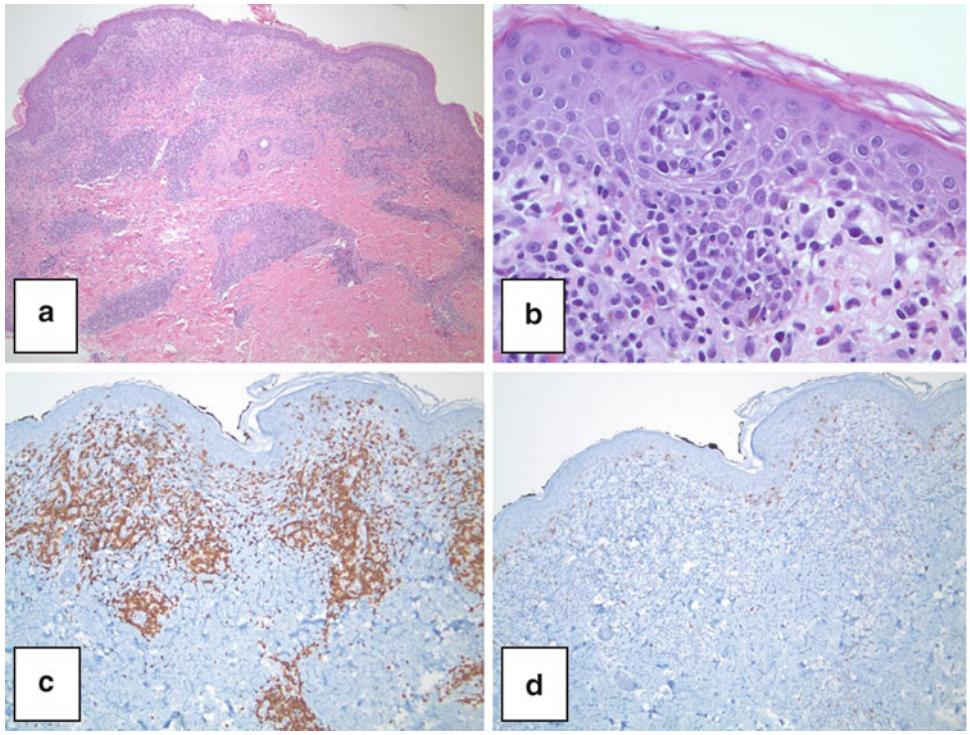

Fig. 1.11 Mycosis fungoides. (**a**) HE ×40. Infiltrate in the superficial dermis, with epidermotropism. (**b**) HE ×400. Pautrier microabscess, in the superficial dermis. The cells in the microabscess are atypical lymphocytes. (**c**) CD3 ×100. Most cells in the infiltrate are T-lymphocytes. (**d**) CD7 ×100. The lymphoma cells show abnormal loss of CD7 expression

a band-like pattern (lichenoid pattern) (Fig. 1.11a). Initially, the MF cells are small or intermediate, with scant-to-moderate cytoplasm and dense, hyperchromatic nuclei with irregular cerebriform contours (Fig. 1.11). Eosinophils and histiocytes are often admixed within the infiltrate. The progression of MF to plaque or tumor stage is generally associated with reduction in epidermotropism. This may be completely lost in the tumor stage, and clinical history may be required to appropriately designate the tumor as MF rather than a non-MF T- cell lymphoma.

Large, transformed cells may be present within the infiltrate. When large cells, with irregular nuclei, vesicular chromatin, and nucleoli, represent more than 25% of total cells, the diagnosis of MF with transformation to large cell lymphoma is recommended [99–101]. Significant diagnostic difficulties are encountered in cases with morphology of MF with large cell transformation at presentation, as the large cells can often be positive for CD30, leading to a morphology and immunophenotype that can overlap that of lymphomatoid papulosis (LyP), primary cutaneous ALCL, and systemic ALCL, ALK negative involving the skin [86]. However, these cases should not be considered ALCL. As the neoplasm progresses, it involves the lymph nodes [102]. Initially, the involved lymph nodes show dermatopathic changes, considered a benign change [103]. Increasing numbers of atypical cells can be recognized either in small clusters or more easily in later stages as overt architectural distortion of the lymph node by clearly neoplastic cells. Proof of involvement in the earliest stages may be found by molecular studies but clinical staging systems do not recommend routine lymph node biopsy (unless pathologically enlarged) or gene rearrangement studies [104, 105]. At advanced stages, the pattern of lymph node involvement may be indistinguishable from that seen in PTCL NOS.

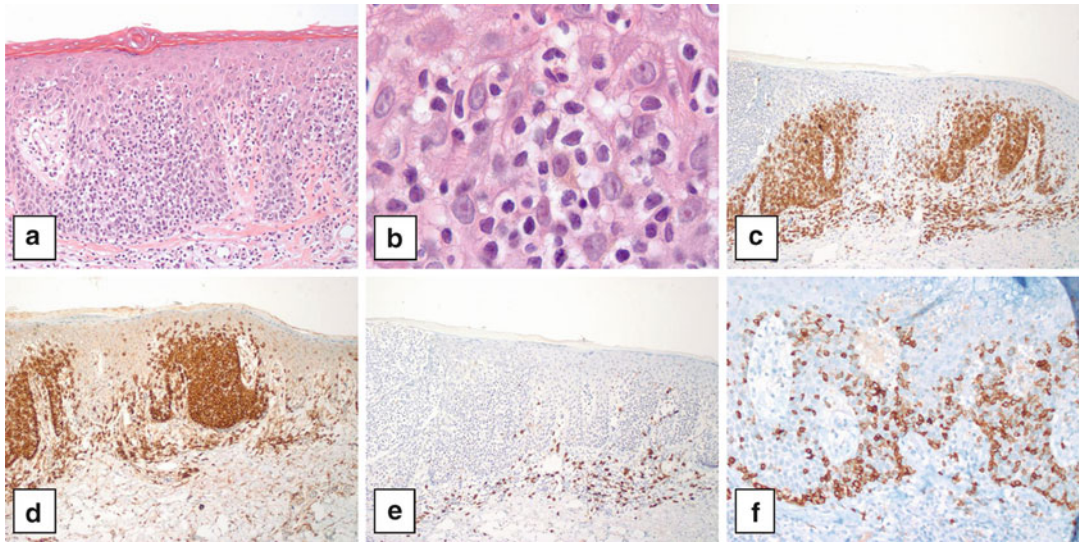

Fig. 1.12 Mycosis fungoides, pagetoid reticulosis. (**a**) HE ×200. Atypical infiltrate with marked epidermotropism and relative sparing of the dermis. (**b**) HE ×1,000. The lymphoma cells are small, with marked nuclear irregularities. (**c**) CD3 ×100. The atypical lymphocytes are CD3+ T-cells. (**d**) CD4 ×100. The lymphoma cells are positive for CD4. (**e**) CD8 ×100. There are very few cytotoxic T-cells in the infiltrate. (**f**) CD30 ×100. Characteristic for this entity, some of the small cells in the infiltrate are positive for CD30

The clinical variants mentioned have morphologic patterns differing from the classical MF (described above). Folliculotropic MF, a variant with a worse prognosis that that of classical MF, is defined by an abundant neoplastic infiltrate in the hair follicles, in the absence of significant involvement of the superficial epidermis [93, 94]. The follicles show mucinous degeneration. In Pagetoid reticulosis (Woringer–Kolopp), the disease is localized and the neoplastic cells infiltrate only the epidermis with sparing of the dermis [95] (Fig 1.12a, b). The rare granulomatous slack skin is characterized by extensive histiocytic and granulomatous proliferation [96, 97].

The immunophenotype of the neoplastic cells is characterized by negativity for CD7 (Fig. 1.11e) in approximately 50% of cases. This feature, however, is not specific as this can occur in some reactive lesions. The MF cells are usually positive for CD2, CD3, CD4, CD5, and CLA (cutaneous lymphocyte antigen). Only rare cases are positive for CD8 [106].

Molecular studies performed on the skin lesions from MF can identify monoclonal T-cell receptor rearrangements. Again, while supportive of lymphoma, uncommon reactive lesions may show monoclonal gene rearrangements. In difficult cases, it may be necessary to study multiple lesions from the same patient over time to demonstrate a persistent malignant clone [107]. There are no characteristic chromosomal abnormalities for MF: in a significant number of cases there are losses of genetic material from 1p, 10q, 17q, 19, gains of 3p25, 8p22, 11q13, 19p13, or numeric abnormalities of 6, 13, 15, 17 [108, 109].

Sezary Syndrome (SS)

Sezary syndrome represents 5% or less of new cases of MF and can be considered the leukemic form of MF. It is clinically aggressive with 5 year survivals in the 10–20% range. The diagnosis of SS implies the triad of erythroderma, generalized lymphadenopathy, and abnormal lymphocytes with characteristic morphology (cerebriform lymphocytes-Sezary cells) in the skin, lymph nodes, and blood [1] (Fig. 1.13). Furthermore, one or more of the following should be present: greater than 1,000 cells/μL Sezary cells, a CD4:CD8 ratio >10 in blood by flow cytometry, loss of pan-T-cell antigens, or demonstration of a

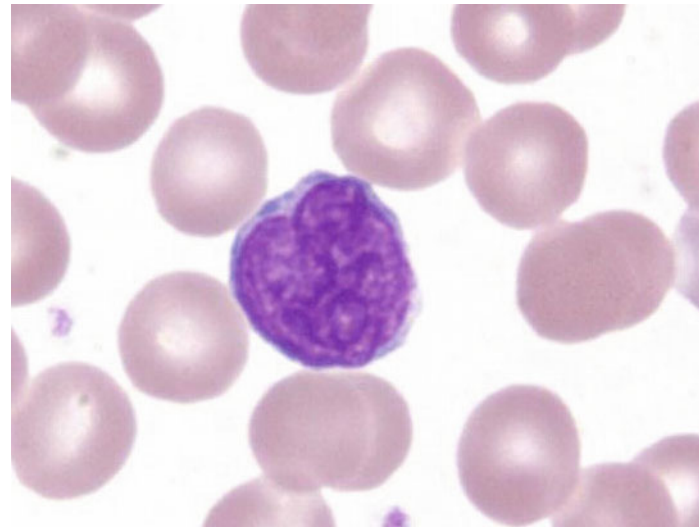

Fig. 1.13 Sezary syndrome. Peripheral blood, Wright–Giemsa ×1,000. The cell has a characteristic "cerebriform" nucleus

T-cell clone by molecular methods [92, 110, 111]. The morphology of the Sezary cells is best appreciated on peripheral blood smears. The cells are usually intermediate sized, with dispersed chromatin and nuclear convolutions; however, small cell variants are described with a more condensed, mature chromatin pattern but retaining the nuclear irregularities.

Primary Cutaneous CD30-Positive T-Cell Lymphoproliferative Disorders

The two entities in this category have significantly overlapping morphologic, immunophenotypic, and molecular features, which make them difficult to differentiate in the absence of an extensive, detailed clinical history [1, 36, 112]. Moreover, advanced stages of MF and cutaneous involvement by systemic ALCL can lead to patterns similar to those in this category.

Primary cutaneous ALCL differs from the nodal ALCL by its initial presentation (exclusively involving the skin) and negativity for ALK [36, 112]. This is a disease of older adults, with male predominance although pediatric cases are described. The cell of origin is not well characterized although it probably is a malignant counterpart of activated T-cells. The clinical course is variable, as spontaneous regression of the lesions can occur. The 5 year survival is over 90% [113].

Grossly, the skin lesions are usually single papules or ulcerated nodules, most >2 cm, but cases with multiple lesions have also been described. Histologically, the malignant infiltrate involves the superficial layers of the skin. The cells are large, with moderate cytoplasm and irregular nuclei, with fine chromatin and conspicuous nucleoli. Variants with smaller cells have been described. In most cases, the neoplastic cells are associated with histiocytes and eosinophils. When associated with ulcerations, the malignant cells can be surrounded by numerous inflammatory cells that can obscure the overall architecture of the infiltrate. A neutrophil-rich variant has been described, and in this variant, the neoplastic cells are a small minority of the lesion [114].

The immunophenotype of c-ALCL is characterized by positivity for CD4, granzyme B, TIA-1, perforin, and CD30. Clusterin is also expressed, with a Golgi dot-like pattern but is not specific as it can be seen in LyP, transformed MF, and some reactive conditions [115]. T-cell markers such as CD2, CD5, or CD3 can be lost. The neoplastic cells are negative for EMA, ALK, or CD15.

Molecular studies show clonal rearrangements of TCR genes. Rearrangements of

BUSP22 occur in up to 57% of cases and may be diagnostically useful [116].

LyP is a self-healing cutaneous lesion. It occurs mainly on the trunk and extremities of adults (median age of 45 years), with a male predominance [113]. The prognosis of these patients is excellent, as most lesions spontaneously regress. However, as there are no reliable prognostic indicators, close clinical follow-up is recommended.

Grossly, the lesions are multiple, small (<2 cm) papules with waxing and waning course, usually at different stages of development [113]. In a small minority of the patients, the lesions are preceded by MF. There are three histologic patterns of LyP [86]: type A with small clusters of pleomorphic, CD30 positive cells on a background of benign reactive cells, type C with sheets of anaplastic CD30 positive cells and limited mixed inflammatory infiltrate, and type B, with an epidermotropic infiltrate of small atypical cells, often negative for CD30.

The immunophenotype of the atypical cells in LyP is similar to those of the cells in c-ALCL, and molecular studies can identify clonal rearrangements of *TCR* genes [117]. *BUSP22* rearrangements are generally absent from LyP lesions [116].

Primary Cutaneous γδ T-Cell Lymphoma

This is a rare neoplasm of gamma-delta cytotoxic T-cells usually confined to the skin (mainly of extremities) and mucosa, mainly diagnosed in adults [118, 119]. A subset of cases can be associated with hemophagocytic syndrome [120]. The cell of origin is considered to be the activated cytotoxic γδ T-cells. This is an aggressive type of lymphoma, with a relatively short median survival (15 months) [120].

Gross examination can show several types of lesions: subcutaneous tumors, patches or plaques, ulcerations [120]. Histologic examination can divide the lesions in epidermotropic, dermal, and subcutaneous tumors. Overall, the pattern of involvement is similar to that seen in SPTCL, with the difference that usually there is significant involvement of dermis in primary cutaneous γδ T-cell lymphoma (PCGDTCL). Epidermis is often also involved and ulceration can be present. The malignant cells are intermediate to large, with dense chromatin. In the subcutaneous fibroadipose tissue, these cells can display adipocyte rimming. Necrosis and apoptosis are often prominent features of these tumors.

The immunophenotype of PCGDTCL is CD2+, CD3+, CD56+, TCRδ+. The cells are negative for CD4, CD5, CD8, βF1 [120].

Molecular studies have shown most of the cases to have clonal *TCR* γ rearrangements [121]. There is very little information on the cytogenetics of these lesions.

Primary Cutaneous CD8-Positive Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma

A provisional entity in the WHO 2008 classification of tumors of hematopoietic and lymphoid tissue, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma, is a rare entity occurring mainly in adults [1, 86]. The cell of origin is the cytotoxic αβ T-cell with skin homing abilities. In contrast with CD4-positive primary cutaneous T-cell lymphoma, as its name suggests, this neoplasm has an aggressive clinical course [122].

Clinical examination shows the patients to have disseminated papules, nodules or tumors, with central necrosis, ulceration and hyperkeratotic plaques. In advanced stages, the tumor shows extensive visceral dissemination [86, 122]. Microscopic examination shows a malignant process with lichenoid pattern and marked epidermotropism. Overall, the pattern can be reminiscent of that of pagetoid reticulosis, with the difference that the lesions are widespread. The epidermis can show reactive changes, such as acanthosis, atrophy, necrosis, spongiosis. As the tumor invades deeper structures, it can display angiocentricity and angioinvasion, sometimes resulting in necrosis. The tumor cells are of variable size, most often small, with irregular nuclei, often with dense chromatin, sometimes with blastic chromatin [86, 122].

The immunophenotype of the lymphoma cells is positive for CD3, CD8, βF1, granzyme B,

perforin, TIA-1. These cells are negative for CD4, CD5, and CD7. In most cases, they are also negative for CD2 [123].

While there are no conventional cytogenetic abnormalities identified to date, molecular studies almost always show clonal rearrangements of the *TCR* genes.

Primary Cutaneous CD4-Positive Small/Medium T-Cell Lymphoma

This is another provisional entity in the WHO 2008 classification [1]. It is a rare tumor defined as a (most often solitary) tumor mass with the appearance of the tumor stage of MF, in a patient without a history of MF, or without patches or plaques [124]. The tumor cells are thought to be malignant counterparts of skin-homing CD4-positive T-cells. This is considered an indolent lymphoma with prognosis of the patients with this type of lymphoma is relatively similar to that of patients with MF.

Gross examination shows usually a single skin nodule. Histologic examination shows a dense infiltrate mainly in the dermis, but also expanding in the subcutaneous tissue and displaying moderate epidermotropism (significantly less than MF). The lymphoma cells are small/intermediate T-cells, with abnormal nuclei, similar to those seen in MF.

The immunophenotype of the malignant cells is positive for CD3, CD4 and is negative for CD8 or CD30.

There are no data on the cytogenetics of this lesion. Molecular studies for clonal *TCR* rearrangements are positive.

T-Cell Prolymphocytic Leukemia

T-cell prolymphocytic leukemia (T-PLL) is an aggressive T-cell neoplasm involving the peripheral blood, lymph nodes, bone marrow, liver, spleen, and skin [1]. The cell of origin is a post-thymic (non-lymphoblastic) T-cell. This neoplasm is most often detected in adult males and has an aggressive course, with a median survival of less than 1 year [125–127]. An early indolent phase has been described, but most patients then enter an aggressive terminal phase [128].

The clinical presentation of T-PLL patients is generalized lymphadenopathy, rapidly increasing lymphocyte counts, hepatosplenomegaly. Cytopenias can be a consequence of bone marrow involvement. In a significant number of cases, the skin is extensively involved [129] (Fig. 1.14b, c).

Histologic examination of the involved tissues does not show a pathognomonic pattern, although sometimes it involves paracortical zones and spares normal structures such as lymphoid follicles in lymph nodes. Usually, the neoplastic infiltrate is composed of small cells, with dense chromatin (Fig. 1.14). Since the morphologic features are not entirely specific, clinical history is important at arriving at the correct diagnosis. On bone marrow or peripheral blood smears, the

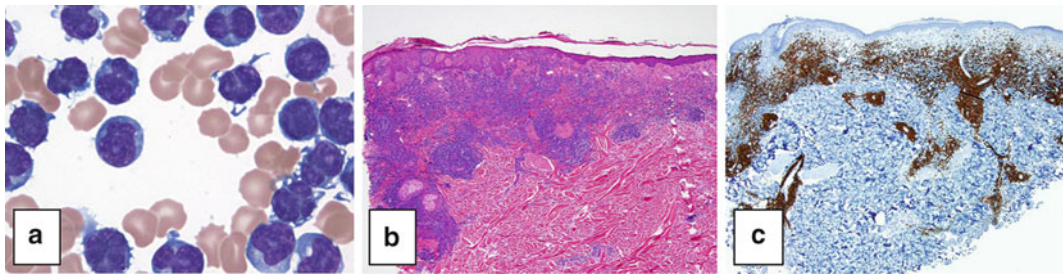

Fig. 1.14 T-cell prolymphocytic leukemia. (**a**) Peripheral blood, Wright–Giemsa ×1,000. Lymphocytosis with small lymphocytes. The nuclei are irregular, with knobs and notches, smudged chromatin, and small nucleoli. Cytoplasmic blebs are visible on the surface. (**b**) Skin, HE ×40. Dense small lymphocytic infiltrate, with limited epidermotropism. (**c**) TCL1 ×40. The lymphoma cells are positive

lymphoma cells are small to intermediate, with light basophilic cytoplasm without granules. The cell surface can show membrane blebbing. The nuclei are irregular, with notches or knobs, relatively dense chromatin, and usually central nucleoli [130] (Fig. 1.14a).

The immunophenotype of T-PLL cells is CD2+, CD3+, CD7+. Most cases (60%) are positive for CD4, 25% of cases are positive for both CD4 and CD8, while rare cases (15%) are positive for CD8 [130]. Another immunophenotypic feature characteristic of T-PLL (in addition to positivity for both CD4 and CD8) is positivity for TCL1, a protein normally expressed in B-cells [131] (Fig. 1.14c).

Molecular studies identify clonal rearrangements of *TCR* γ or β genes. Genetic abnormalities include inv(14)(q11q32) or t(14;14)(q11;q32) [125, 132]. The results of these abnormalities is the transposition of *TCL1A* and *TCL1B* in the *TCR* α gene locus (and hence their overexpression). A variant translocation is t(X;14)(q28;q11), resulting in the translocation of *MTCL1*. Other abnormalities described in T-PLL are idic(8p11), t(8;8)(p11-12;q12) and trisomy 8q. The observation that T-PLL is more frequent in patients with ataxia-telangiectasia has let to the identification of missense mutations of ATM (at 11q23). A minority of cases has mutations on chromosomes 6 or 17 [133].

T-Cell Large Granular Lymphocytic Leukemia

T-cell large granular lymphocytic leukemia (T-LGLL) is defined as an increase in circulating large granular lymphocytes lasting usually over 6 months and in most cases reaching levels of $2–20 \times 10^9$/L [1]. Most patients are adults, with no sex predilection. The disease is most often indolent with a prolonged course, characterized by cytopenias, splenomegaly. Many patients also have rheumatoid arthritis, circulating immune complexes, or other abnormalities of the immune system. Recent studies have shown a propensity for coexistence of B-cell dyscrasias including monoclonal gammopathy of undetermined significance, monoclonal B-cell lymphocytosis, and overt B-cell lymphoma/leukemia [134, 135]. Clones of cytotoxic T-cells have also been described in post-transplant patients. The cells of origin are cytotoxic T-cells, either CD8 positive or γδ. With the exception of rare cases with an aggressive course, T-LGLL is an indolent disease, with a protracted clinical course [136–139].

In the peripheral blood, the abnormal T-LGLs have features relatively similar to those of normal T-LGLs, but the granules can be more coarse or less numerous. The bone marrow can be normocellular (in most cases) or hypocellular. The T-LGLs can form aggregates, but most often are diffusely distributed, mainly with an intra-sinusoidal pattern. Benign lymphoid aggregates can also be present and could signal abnormal immune processes [140].

The cytotoxic cells are positive for CD2, CD3, CD5, CD7, CD8, CD16, CD57. Rarely CD5 or CD7 can be lost. Cytotoxic molecules such as granzyme B, perforin, TIA-1 are a constant feature. Very few cases are positive for CD4 (but not for co-expression of CD4 and CD8). TCR-Vbeta analysis shows restricted Vbeta family usage, and KIR analysis shows restricted KIR patterns [141]. Electron-microscopy shows the granules to be tubular array filled with proteins, probably cytotoxic.

Conventional cytogenetic analysis of T-LGLL is usually noncontributory, but when abnormalities are identified they are nonspecific. Molecular studies show *TCR* γ chain rearrangements [137]. Recently, somatic mutations in STAT3 have been found in 30- 40 % of T-LGLL cases [142].

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