Pathology of T-Cell Lymphomas: Diagnosis and Biomarker Discovery

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Abstract

T-cell lymphomas are a group of predominantly rare hematologic malignancies that tend to recapitulate different stages of T-cell development, in a similar way that B-cell lymphomas do. As opposed to B-cell lymphomas, the understanding of the biology and the classification of T-cell lymphomas are somewhat rudimentary, and numerous entities are still included as 'provisional categories' in the World Health Classification of hematolopoietic malignancies. A relevant and useful classification of these disorders have been difficult to accomplish because of the rarity nature of them, the relative lack of understanding of the molecular pathogenesis, and their morphological and immunophenotypical complexity. Overall, T-cell lymphomas represent only 15 % of all non-Hodgkin lymphomas. This review is focused on addressing the current status of the categories of mature T-cell leukemias and lymphomas (nodal and extranodal) using an approach that incorporates histopathology, immunophenotype, and molecular understanding of the nature of these disorders, using the same philosophy of the most recent revised WHO classification of hematopoietic malignancies.

Keywords

T-cell lymphoma · Non-Hodgkin lymphoma · WHO classification

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Contents

1 Introduction

T-cell lymphomas are a group of predominantly rare hematologic malignancies that tend to recapitulate different stages of T-cell development, in a similar way that B-cell lymphomas do. As opposed to B-cell lymphomas, the understanding of the biology and the classification of T-cell lymphomas is somewhat rudimentary, and numerous entities are still included as 'provisional categories' in the World Health Classification of hematopoietic malignancies [1]. A relevant and useful classification of these disorders has been difficult to accomplish because of their rarity, the relative lack of understanding of the molecular pathogenesis, and their morphological and immunophenotypical complexity [2]. Overall, T-cell lymphomas represent only 15 % of all non-Hodgkin lymphomas [2, 3].

In the recent years, many developments in immunology and molecular biology have provided tools to subclassify these disorders, using an approach that will benefit targeted therapy. In this sense, peripheral T-cell lymphomas (PTCL) not otherwise specified, an old waste basket category with an overall poor prognosis, have emerged with subsets of follicular T-helper (FTH) differentiation [2, 4] with an overall better prognosis. In addition, studies have determined an important prognostic value in distinguishing cases of ALK− anaplastic large cell lymphoma (ALCL) from PTCL as the former appear to have better prognosis and could benefit from certain forms of therapy [3–8]. Certain site-specific forms of ALCL (not yet incorporated into the WHO classification), such as ALCL associated with breast implants, can be completely indolent and not require additional forms of therapy other than removing the implants [9, 10]. The classification schemes that, are already difficult and of limited value for systemic T-cell lymphomas, are even more problematic for the cutaneous T-cell lymphomas (CTCL), where other than mycosis fungoides (MF), Sézary syndrome (SS), cutaneous ALCL, and subcutaneous panniculitis-like T-cell lymphoma (SPTCL), the remaining subtypes are currently still at the 'provisional' stage.

This review is focused on addressing the current status of the categories of mature T-cell leukemias and lymphomas (nodal and extranodal) using an approach that incorporates histopathology, immunophenotype, and molecular understanding of the nature of these disorders, using the same philosophy of the most recent

Table 1 WHO classification of mature T/NK-cell leukemias and lymphomas

Mature leukemias
• T-cell prolymphocytic leukemia
• T-cell large granular lymphocytic leukemia
• Chronic lymphoproliferative disorders of NK-cells
• Aggressive NK-cell leukemia
• Adult T-cell leukemia/lymphoma
• Sezary syndrome
Mature Lymphomas
• Extranodal NK/T-cell lymphoma, nasal type
• Enteropathy-associated T-cell lymphoma
• Hepatosplenic T-cell lymphoma
• Peripheral T-cell lymphoma, not otherwise specified
• Angioimmunoblastic T-cell lymphoma
• Anaplastic large cell lymphoma (ALCL), ALK positive
• Subcutaneous panniculitis-like T-cell lymphoma
• Mycosis fungoides
• Primary cutaneous anaplastic large cell lymphoma (C-ALCL)
• Lymphomatoid papulosis
Provisional categories
• Primary cutaneous gamma–delta T-cell lymphoma
• Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
• Primary cutaneous CD4−positive small/medium T-cell lymphoma
• Anaplastic large cell lymphoma, ALK negative

revised WHO classification of hematopoietic malignancies. The current accepted and provisional categories of T-cell and NK-cell lymphomas are detailed in the Table 1 [1, 11].

1.1 Mature T-Cell Leukemias

1.1.1 T-Cell Prolymphocytic Leukemia (T-PLL)

Clinical and Epidemiologic Features

T-cell prolymphocytic leukemia is a rare, predominantly aggressive disorder, accounting for 2 % of the mature lymphoid leukemias. The median age at presentation is 65 years, and clinically, most patients have generalized disease with hepatosplenomegaly, generalized adenopathy, and a striking lymphocytosis (>100 × 10^9/l) [12–16]. Cutaneous dissemination is very common, and particularly in the form of a facial rash, which can be present in up to 20 % of patients. Sometimes, the rash is the first clue to the diagnosis [13, 17, 18]. Serologies for

HTLV are negative, but rare cases have been reported as positive [19]. The prognosis has been a matter of debate: Most cases have an aggressive course, with a survival of less than 1 year, but others have shown a more indolent clinical course [13–15, 20].

Histopathology, Immunophenotypic, and Molecular Features

The morphologic features (Fig. 1) of T-PLL are vital to make a diagnosis. It is recognized that this type of leukemia can have a broad morphologic spectrum of findings: In half of the cases, the cells have a round-to-oval nucleus, and the remainder can be irregular and somewhat cerebriform [14, 21]. Most cases show a predominance of prolymphocytic cells with condensed chromatin and prominent nucleoli. The cytoplasm is basophilic and agranular and can show 'blebs.' In 20 % of cases, the cells are much smaller and with more inconspicuous nucleoli. This is referred to as 'small cell variant of T-PLL.' A cerebriform variant, morphologically similar to the cells of SS can be seen in 5 % of cases [12–14, 16, 22]. Tissue diagnosis is not essential for its diagnosis: In the bone marrow, there are diffuse and interstitial infiltrates accompanied almost invariably by reticulin fibrosis. In most lymph node biopsies, there is an abnormal paracortical expansion of neoplastic T cells. Skin should be evaluated carefully: The infiltrates in T-PLL tend to be superficial and deep with a perivascular and interstitial distribution and spare the epidermis, as opposed to most primary CTCL [17, 18, 23].

Immunophenotypically, T-PLL is a mature T-cell leukemia (TdT and CD1a negative), while CD2, CD3, and CD7 are positive. Nearly 80 % of cases express CD4 and, of those, 65 % do not have coexpression of CD8 (CD4+/CD8−), 21 % have coexpression of both CD4+/CD8+, approximately 17 % were CD8+/CD4− [12], and 3.4 % are CD4−/CD8−. Rare cases can show a switch from CD4 to CD8 [22, 24]. Most cases have high levels of CD52 expression, providing a rational for treatment with alemtuzumab [15, 25–28]. CD25, CD38, and HLA-DR are variably expressed. The distinctive coexpression of CD4/CD8, weak membrane CD3, and strong CD7 suggests that T-PLL represents an intermediate stage of differentiation between a cortical thymocyte and a circulating mature T cell. Nearly all cases will have rearrangements of the TCR-β- or γ-genes.

T-PLL shows complex cytogenetic aberrations: Inversion (14)(q11;q32) is characteristic of the disease and present in more than 2/3 of cases [14, 15]. Tandem translocations between the 2 chromosomes 14, t(14;14) can also occur. The rearrangements involve the *TCR-α* and protooncogene *TCL-1*. 20 % of patients have a t (X;14) translocation. Abnormalities involving both arms of chromosome 8 are frequent, and overexpression of the c-myc protein is found in cases with iso8q. While the 14q abnormality and trisomy 8q are common in Western countries, they are rarely seen in Japan [20]. Although 11q23 abnormalities are seldom detected on cytogenetics, molecular analysis frequently detects mutations of the *ATM* gene [29]. Since these cytogenetic aberrations are believed to be incapable of leukemogenesis, more recently mutations in *JAK1* and *JAK3* have been found in up to 34 % of cases of T-PLL [30, 31]. JAK3 is directly linked to T-cell maturation. Abnormalities of

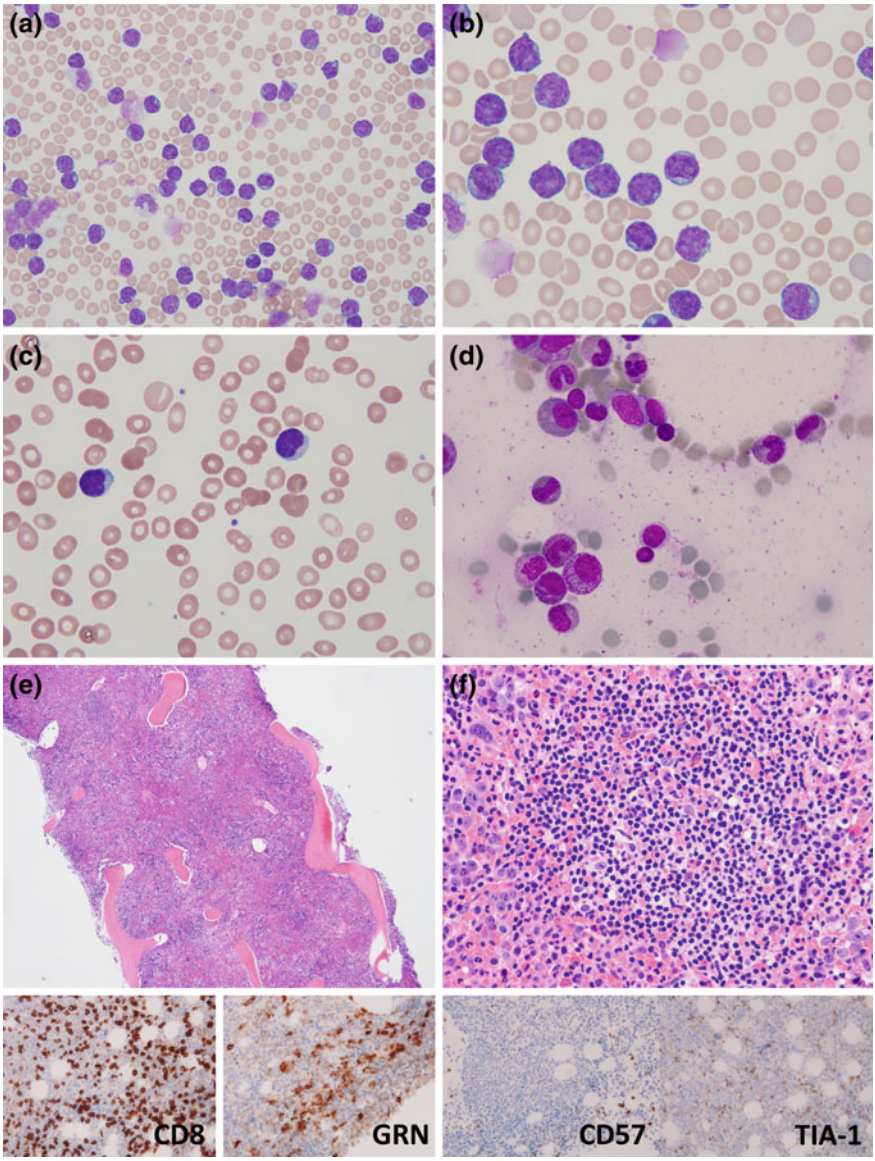

Fig. 1 **a**–**b**, T-cell prolymphocytic leukemia. The small-to-medium-sized cells show nuclear contour irregularities and 'blebbing,' with distinctive prominent nucleoli. **c** (PBL) and **d** (aspirate) T-LGL. The cells are small to medium, with irregular borders, with abundant cytoplasm with granules. **e** and **f** T-LGL involving the bone marrow. Interstitial and nodular aggregates of lymphoid cells. The atypical cells are positive for CD8, granzyme B (GRN), CD57 (weak), and TIA-1. The pattern of involvement in sinusoidal

chromosomes 22q11, 13q, 6q, 9p, 12p, 11p11-p14, and 17p have also been shown by chromosome analysis and aCGH [14, 32].

1.1.2 T-Cell Large Granular Lymphocytic Leukemia (T-LGL)

Clinical and Epidemiologic Features

T-LGL accounts for less than 5 % of all mature leukemic lymphoproliferative disorders [2, 33–35] with a mean age of 50–60. There is a slight higher prevalence of the disease in Asians, where appears to be more commonly associated with anemia [36, 37]. T-LGL is commonly associated with rheumatoid arthritis (20 % of cases) and some lymphoproliferative disorders such as CLL/SLL and monoclonal B-cell lymphocytosis (10–20 %). Other rheumatologic processes can be seen in association, and nearly half of patients with T-LGL have a positive rheumatoid factor or polyclonal hypergammaglobulinemia [38–46]. Rare cases present after transplantation [47, 48].

Originally, a large granular lymphocytosis of $>2 \times 10^9$/L was proposed as a diagnostic criterion but, since a third of cases show $<1 \times 10^9$/L, this is no longer needed for a diagnosis [49, 50]. Bone marrow involvement is seen in 75 % of cases and mild splenomegaly in 15–50 %. Rarely, there might be pulmonary hypertension, which appears to be linked to damage to the vascular endothelium [51]. Neutropenia is a very common feature and present in 60–70 % of cases, while thrombocytopenia is very rare. Anemia can be as frequent as neutropenia, and some cases can present with red cell aplasia [52]. T-LGL does not involve the lymph nodes, and if present, the diagnosis should be reconsidered [53].

Histopathology, Immunophenotypic, and Molecular Features

The classic morphologic features of T-LGL (Fig. 1) account the presence of lymphoid cells with abundant cytoplasm (which represent the 'large' character of the cells), minimal nuclear enlargement, nuclear contour irregularities, and the presence of cytoplasmic granules [21]. However, in some cases, the cytoplasm might be sparse and the granules not as prominent. The pattern of bone marrow involvement is sinusoidal (80 % of cases), which is best demonstrated with immunostains. However, interstitial aggregates of reactive T cells can be seen in up to 15–50 % of cases [54, 55]. In the spleen, there are both red pulp and perivascular white pulp involvements [54, 55]. Likewise, in the liver, there is usually a sinusoidal infiltrate of abnormal T cells. It is widely accepted that large cell transformation is not a feature of T-LGL.

Immunophenotypically, T-LGL is a disease of CD8+ cytotoxic T cells with TCRαβ expression, with isolated case reports of T-LGL with a CD4 phenotype [56]. A subset of cases with CD4−/CD8− T-LGL have a higher prevalence of anemia [57]. Diminished expression of CD5 and CD7 is common. Coexpression of NK cell associated antigens is universal to some extent, and in particular for CD16 and CD57 (one or both are found in >80 % of cases). CD56 is not commonly seen, as opposed to hepatosplenic T-cell lymphoma (HTCL). CD57 expression by

immunohistochemistry is only seen in <20 % of bone marrow specimens [58, 59]. Strong homogeneous expression of CD16 appears to be more useful when compared to CD57. Abnormal expression of Killer-cell immunoglobulin-like receptor antigens (KIR) can be seen in 50 % of T-LGL [59, 60]. CD335 is also positive in T-LGL [61].

The vast majority of cases of T-LGL show no cytogenetic aberrations. Deletion of 6q, translocations and inversions involving the T-cell receptor loci on chromosomes 7 and 14 has been rarely described [62]. At a molecular level, most cases show clonality by PCR or flow cytometric analysis. However, as opposed to other T-cell lymphoproliferative disorders, T-LGL lacks the homogeneity of the clones. Most cases appear to be actually oligoclonal [63]. Molecular pathways that appear to be altered in T-LGL include resistance to *FAS* and activation of STAT3 pathway [41–43, 45, 46]. The *STAT3* mutations are present in a 1/3 of T-LGL cases. STAT3 is involved in cell proliferation, apoptosis, angiogenesis, and immune responses. STAT3, a latent transcription factor, has been shown to play a central role in conferring cell survival [46].

1.1.3 Adult T-Cell Leukemia/Lymphoma (ATLL)

Clinical and Epidemiologic Features

Adult T-Cell Leukemia/Lymphoma (ATLL) is a mature T-cell leukemia, which its pathogenesis is linked to the infection with human T-cell leukemia virus type-1 (HTLV-1) [64]. It is more commonly seen in areas where the infection with the virus is endemic, particularly in Japan, the Caribbean, parts of central Africa, South America, and Iran [65, 66]. The majority of the individuals who develop the disease do so after a very long latency period. In some areas of Japan, the prevalence ranges from 0.3 to 13 % of the population [67]. The cumulative incidence of ATLL is estimated to be 2.5 % of those individuals infected by HTLV-1. ATLL is only present in adults, at a mean age of 58, with a slightly higher prevalence in male.

Most cases of ATLL present with widespread disease including lymph node and peripheral blood involvement. The degree of bone marrow involvement does not correlate with the burden of disease in the blood, suggesting that the tumor cells are recruited from other sites. In fact, the skin is a very common site of involvement (>50 %) [65, 68–70]. The cutaneous manifestations are diverse including erythema, papules, nodules, and rarely erythroderma. Other extranodal sites of involvement include the lung, liver, spleen, GI tract, and CNS [65, 71, 72]. Different variants have been described according to the Japanese lymphoma study group [73]: Those include smoldering, chronic, acute (leukemic), and lymphomatous. The most common form is the leukemic (60 %), typically accompanied by significant leukocytosis, rash, generalized lymphadenopathy, hypercalcemia, and lytic bone lesions. Even in the setting of marked leukocytosis, bone marrow involvement may be absent. Additional opportunistic infections are also frequent. The lymphomatous (20 %) variant does not show peripheral blood involvement, and hypercalcemia is infrequent. The survival in the acute and lymphomatous variants is very poor

(2 weeks–1 year). The chronic variant (15 %) presents with a rash, leukocytosis, fewer numbers of circulating tumor cells and prolonged survival. The smoldering variant (5 %) has a normal WBC, skin lesions, and no systemic disease. This form can evolve into the more advanced presentations in 25 % of cases [65, 68, 73].

Histopathology, Immunophenotypic, and Molecular Features

ATLL (Fig. 2) shows a protean morphology [64, 65, 68, 74–76]. The classic features associated with the disease include neoplastic lymphoid cells, which are polylobulated, hyperchromatic, with nuclear convolutions, and have been termed as 'flower cells.' The cells do not have a prominent nucleolus and have a classic basophilic cytoplasm (useful features to distinguish from Sézary cells). Numerous morphologic variants have been described: pleomorphic, anaplastic, and a rare variant resembling angioimmunoblastic T-cell lymphoma (AITL) [77].

The architecture of the lymph nodes is completely effaced, and some cases can show a sinusoidal pattern of involvement. Eosinophilia in the background can be prominent. Blast-like cells with transformed nuclei and dispersed chromatin are also present. Giant cells with bizarre and cerebriform nuclei can be seen. Some cases have features indistinguishable from ALCL (but are ALK) [53, 65, 68, 74]. Hodgkin-like histology has also been described [78, 79]. The cutaneous histopathologic findings are equivalent to those seen in cases of MF [70], including the presence of Pautrier microabscesses [74, 80]. Some unusual variants in a cutaneous site include folliculotropic (follicular mucinosis) [81], pagetoid reticulosis-like [82], and vesiculobullous [83]. Within the bone marrow, the infiltrate might be subtle, typically interstitial, and osteoclastic activity might be prominent. In the liver, the infiltrates are portocentric, and interface hepatitis can be present.

Immunophenotypically, the tumor cells express T-cell markers and typically have marked decreased expression of CD7. Most cases are CD4+/CD8−, some are CD4−/CD8+ and also CD4+/CD8+. CD25 and IL-2R are expressed in nearly all cases. CD30 can also be positive. ALK and cytotoxic molecules are negative [84]. CCR4 and FOXP3 are expressed in 68 % of cases [85, 86]. The combination of these markers suggests T regulatory phenotype. Targeted therapy for anti-CCR4 is currently in clinical trials [87–89].

At a molecular level, there is a clonal population of T cells with integration of the HTLV-1 virus into the neoplastic cells. Oligoclonal populations of T cells can be seen in HTLV-1 carriers. The viral protein Tax has been shown to be critical for leukemogenesis [90]. More recently, the viral basic leucine zipper factor (HBZ) has been shown overexpressed in all leukemic cases [91–96], and it appears to be the most important gene in the pathway to malignant transformation. HBZ is linked to cell proliferation, but also reacts with Smad2/3 and p300 proteins and enhancing the transcription of the *HBZ* gene. More than 80 % of cases show aneuploidy, and there is no distinctive cytogenetic alteration [97]. Overexpression of BIRC5 can be seen, and it is linked to resistance to chemotherapy [98].

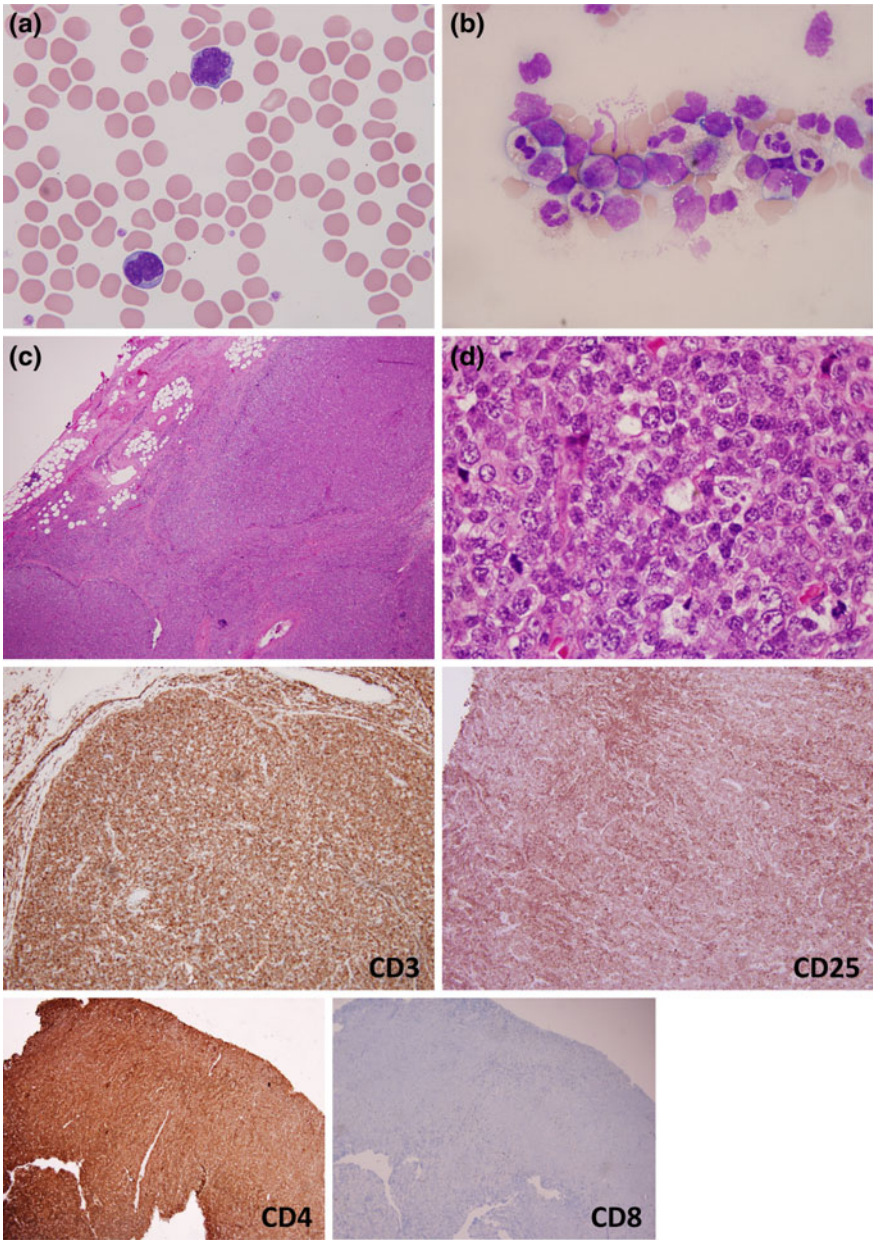

Fig. 2 **a** (PBL) and **b** (aspirate): malignant lymphoid cells in ATLL. The cells show a 'flower-like' appearance. **c–d** lymph node involvement by ATLL. The tumor cells efface the architecture and are medium to large in this pleomorphic variant. The malignant cells are positive for CD3, CD25 and CD4, but negative for CD8

1.1.4 Sézary Syndrome (SS)

Clinical and Epidemiologic Features

SS is defined as a separate entity by the WHO/EORTC classification and is an aggressive disease [99, 100]. SS is characterized by circulating atypical T cells (Sézary cells), erythroderma, and pruritus with or without lymphadenopathy [101]. Most cases present de novo, over a short period of time, but some can have a prodrome of pruritus and non-specific dermatitis. It may follow classic MF. It has been proposed that these should be classified as 'SS preceded by MF' to separate from classic MF [102]. Erythrodermic MF usually follows MF and is distinguished from SS by absent or minimal blood involvement. The clinical features of SS range from mild erythema, to generalized diffuse erythroderma with involvement of the palms and soles. Males are affected more commonly. Other common clinical features include alopecia, ectropion, and onychodystrophy.

Histopathology, Immunophenotypic, and Molecular Features

The histologic features of SS are variable and often subtle in the skin. The epidermotropic T cells, Pautrier microabscesses, and haloed lymphocytes are less prominent. Some cases can just present with a perivascular lymphoid infiltrate (Fig. 6) [103, 104]. The detection and quantification of Sézary cells for the diagnosis of SS and MF with leukemic involvement have traditionally been determined by their morphologic identification on peripheral blood smears. Sézary cells have characteristic cerebriform nuclei. This has largely been replaced by flow cytometry because of high interobserver variability in cell counts. In addition, atypical lymphocytes with cerebriform nuclei can be found in the blood of healthy individuals and those with benign inflammatory skin diseases.

Most cases show expression of T-cell antigens (CD2, CD3, CD5) and CD4. Rare cases can be CD8 positive or even CD4+/CD8+ [105]. Most typically the abnormal cells lack CD7 and CD26 [106–109]. Some inflammatory dermatoses unfortunately can show this abnormal phenotype.

At a molecular level, in advanced stage MF and SS, there is a switch from Th1 cytokines to Th2. Th2 cytokines, such as IL-4, IL-5, IL-10, and IL-13, correlate with eosinophilia, erythroderma, high levels of IgE, immunosuppression, and increased susceptibility to bacterial infections. Additional studies have also revealed that MF and SS arise from different memory T-cell subsets. The malignant T cells in SS are of central memory and capable of circulating between skin, lymph nodes, and blood [107, 110–112]. Expression of tissue addressins such as CLA and the lack of L-selectin/CCR7 coexpression are characteristics of effector memory T (Tem) cells [113]. Amplification of the *JUNB* gene has been identified in SS [114–116]. *JUNB* is involved in cell differentiation, proliferation, and apoptosis. In SS, the Th2 phenotype is linked to overexpression of GATA3 and CTLA-4. Impaired proteasome function, with altered degradation of GATA3, has been shown in SS patients [117]. The immunologic disturbances seen in SS impair the function of plasmacytoid dendritic cells, features that constitute a rational explanation for the

immune suppression associated with SS [118, 119]. By aCGH, the most common abnormalities are gains in 8q and 17q and losses at 17p and 10q [120, 121]. Using the same methodology and hierarchical clustering, SS appears to be a distinctive group separated from transformed MF and cutaneous ALCL [122]. A membrane molecule that belongs to the CD28/CTLA-1 receptor family, programmed death-1 (PD-1), may have utility in the identification of SS. Engagement of PD-1 on T cells with its ligand has been shown to inhibit T-cell activation and proliferation. Recent studies have shown a high expression of PD-1 by neoplastic T cells in SS but not MF [123].

1.2 Nodal and Extranodal Mature T-Cell Lymphomas

1.2.1 Anaplastic Large Cell Lymphoma, ALK Positive (ALK+ ALCL)

Clinical and Epidemiologic Features

ALK+ ALCL is a mature T-cell lymphoma with expression of CD30 and ALK1, and a rearrangement of the *ALK1* gene. It is the second most common subtype of PTCL (25 %) and accounts for 5 % of NHL. It is the most common subtype of PTCL in children and accounts for 10–30 % of all pediatric lymphomas [124–126]. Most cases present as lymphadenopathy, and the most common extranodal site is the skin. Other affected sites include bone, lung, liver, and soft tissues [127]. A leukemic presentation is rare and more frequent in the small cell variant [128]. The bone marrow is affected in a small percentage (10–30 %) of cases [129].

Histopathology, Immunophenotypic, and Molecular Features

The classic morphologic picture (Fig. 3) of ALCL includes the so-called hallmark cell: This is a large cell with a pleomorphic, horseshoe-shaped nuclei, a prominent central golgi zone, and abundant cytoplasm [53]. A wreath-like appearance of the cells can also be seen. The tumor cells are usually located around vessels. The typical pattern of lymph node involvement in ALK+ ALCL is sinusoidal, where the tumor cells surround residual lymphoid follicles. Certain histologic variants are recognized in the WHO: (a) lymphohistiocytic (10 % cases) [130, 131] with abundant histiocytes sometimes obscuring the malignant cells and rarely erythrophagocytosis; (b) small cell variant (5–10 % of cases) [132] with a worse prognosis and more frequent leukemic forms [133]; (c) Hodgkin-like variant (3 % of cases) that mimics classical HL [134] and a nodular sclerosing variant. The tumor cells in this variant lack the very large, prominent cherry red nucleoli seen in RS cells. In 15 % of cases, there is a combination of patterns. More uncommon variants include multinucleated giant cells, sarcomatoid, and myxoid forms [124–127]. A novel cutaneous-only form of ALK+ ALCL has been proposed [135].

The immunophenotype must demonstrate the presence of CD30 and ALK expression. In the majority of the cases, there is loss of multiple T-cell antigens

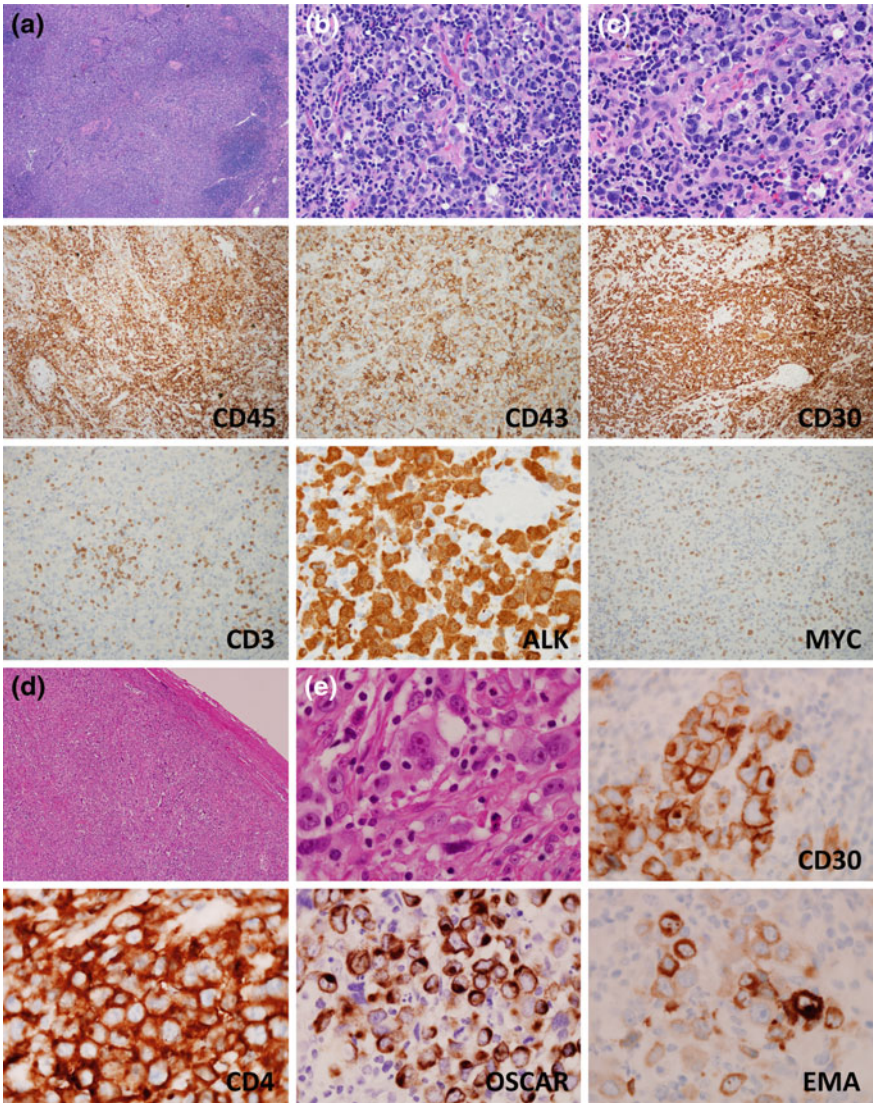

Fig. 3 **a–c** ALK+ ALCL with a typical sinusoidal pattern. The classic cells in this tumor are the so-called hallmark cells. The tumor cells are positive for CD45, CD43, CD30, ALK (nuclear and cytoplasmic patterns), and MYC. The tumor cells have loss of CD3. **d–e** ALK− ALCL, with a similar type of histology to ALK+. In this particular case, there is coexpression of CD30, CD4, EMA, and aberrant expression of keratins (OSCAR)

[136]. CD2 and CD4 are most frequently preserved. Some cases can be positive for TCR receptors. The cytotoxic markers (perforin, TIA-1, and granzyme B) are expressed [137]. The majority of ALCL is positive for EMA. Rare cases can be

CD15+ [138]. Other aberrant markers than can be expressed are cytokeratins, PAX5, CD13, and CD33.

By cytogenetics and FISH, ALK+ ALCL has rearrangements of the *ALK* gene on 2p23 with various partner genes, most typically the nucleophosmin (*NPM*) on 5q35 [139, 140]. Some translocations can be cryptic and not picked up on conventional cytogenetic studies. The cellular localization of the ALK expression correlates with the pattern of translocation: The *NPM/ALK* fusion leads to both nuclear and cytoplasmic staining for ALK; less common partners lead to diffuse cytoplasmic only staining (e.g., *TPM3, ATIC, TFG, TPM4, MYH9, ALO17*), granular cytoplasmic (*CLTC*) or membranous (*MSN*). The translocation partner is not required for a diagnosis, and using a break-apart FISH probe for *ALK* is the most common modality for diagnosis. EBV is not present in ALK+ ALCL, and invariably there is clonality by PCR methods. Inhibitors of the *ALK* gene are currently under investigation for the treatment of relapsed disease [141]. Minimal residual disease assessment using PCR is also being used. Rare cases with rearrangements of the *MYC* gene have also been described [142].

1.2.2 Anaplastic Large Cell Lymphoma, ALK Negative (ALK− ALCL)

Clinical and Epidemiologic Features

In the current WHO, this neoplasm remains under a provisional category. ALK− ALCL is a mature T-cell lymphoma with CD30 expression, morphologically identical to ALK+ ALCL but lacks the expression of ALK. It represents 40–50 % of all ALCLs, but occurs in the older population, predominantly in the sixth decade [143]. The affected individuals present with lymphadenopathy, and extranodal involvement is very rare [144, 145]. Most patients have advanced disease (stage III or IV) and B-symptoms. Because cutaneous ALCL (C-ALCL) and systemic forms are morphologically and immunophenotypically identical (and C-ALCL can extend locoregionally to lymph nodes), the clinical information is imperative [146] to distinguish between the two.

Histopathology, Immunophenotypic, and Molecular Features

The cytology of the tumor cells is identical to ALK+ ALCL but, in general, the tumor cells tend to be larger and more pleomorphic than its ALK+ counterpart (Fig. 3). Multinucleated wreath-like forms are frequent. Histologic variants are not strictly defined, but some cases resemble the lymphohistiocytic variant and others the Hodgkin-like forms [53]. The background cells can include histiocytes, plasma cells, eosinophils, and small lymphocytes [143, 144]. A small cell variant is not typical and, when present, should be classified as peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS). Emphasis in distinguishing ALK− ALCL from PTCL should be placed, as most cases of ALCL will potentially benefit from bone marrow transplant and appear to have a relative better prognosis [8, 143, 144, 147, 148]. A recently described form of ALCL, occurring in association with breast

implants, has a much more indolent behavior and potentially does not require further treatment other than removal of the implants [10]: To this respect, two clinical presentations have been noted: one with an effusion, no mass effect and ± capsule contracture; and a second one with mass effect and ± effusion [149].

The immunophenotype of ALK− ALCL shows strong and diffuse expression of CD30. The pattern can be membranous, Golgi and/or cytoplasmic. The strong and diffuse character is often a helpful clue to distinguish it from PTCL. It often lacks multiple T-cell antigens, and cytotoxic markers are often expressed. EMA and clusterin can be positive, but to a lesser extent than in ALK+ ALCL [145]. Cytokeratin expression can sometimes lead to a misdiagnosis of metastatic carcinoma [150]. At the molecular level, rearrangements of the *DUSP22-IRF4* locus have been described [151–153]. The most common partner is *FRA7H* at 7q32. 6p25.3 rearrangements are mutually exclusive of ALK translocations. They are classically seen in C-ALCL, but can be seen in ALK− ALCL in 18 % of cases.

1.2.3 Angioimmunoblastic T-Cell Lymphoma (AITL)

Clinical and Epidemiologic Features

AITL was originally described as an abnormal immune reaction or form of atypical hyperplasia [154–158]. It is now regarded as a mature T-cell lymphoma. This lymphoma subtype occurs in adults and has not been described in children. Clinically, most patients present with generalized adenopathy, hepatosplenomegaly, skin rash, and prominent constitutional symptoms [159, 160]. Other extranodal sites, such as lung and bone marrow, are also frequently involved. Patients can have polyclonal hypergammaglobulinemia (>50 % of cases) and Coombs-positive autoimmune hemolytic anemia. LDH levels are usually high. In addition, recurrent opportunistic infections may occur.

Histopathology, Immunophenotypic, and Molecular Features

The nodal architecture is typically effaced with open and sometimes dilated sinuses. There is a very striking proliferation of postcapillary or high endothelial venules with prominent arborization (Fig. 4). A dendritic cell proliferation (FDC) around the high endothelial venules is typical. The neoplastic lymphoid cells have clear cytoplasm, and are associated with small lymphocytes, immunoblasts, plasma cells, and histiocytes [53]. Three patterns are now recognized: In pattern 1 (15 % of cases), partial preservation of the architecture with hyperplastic B-cell follicles and a paracortical expansion of T cells and prominent vascularity is seen. In pattern 2 (25 % of cases), there is loss of the architecture with atrophic follicles and concentrically arranged FDC. In pattern 3 (60 %), there is total loss of the architecture with no residual follicles [6, 34, 160–162]. The histologic features in extranodal sites can be relatively non-specific: In the skin, the infiltrate is superficial and deep, and usually spares the epidermis [163–165]. But occasionally, epidermotropic cases mimicking MF have been seen [166]. Cases resembling marginal zone B-cell lymphomas have been reported [167].

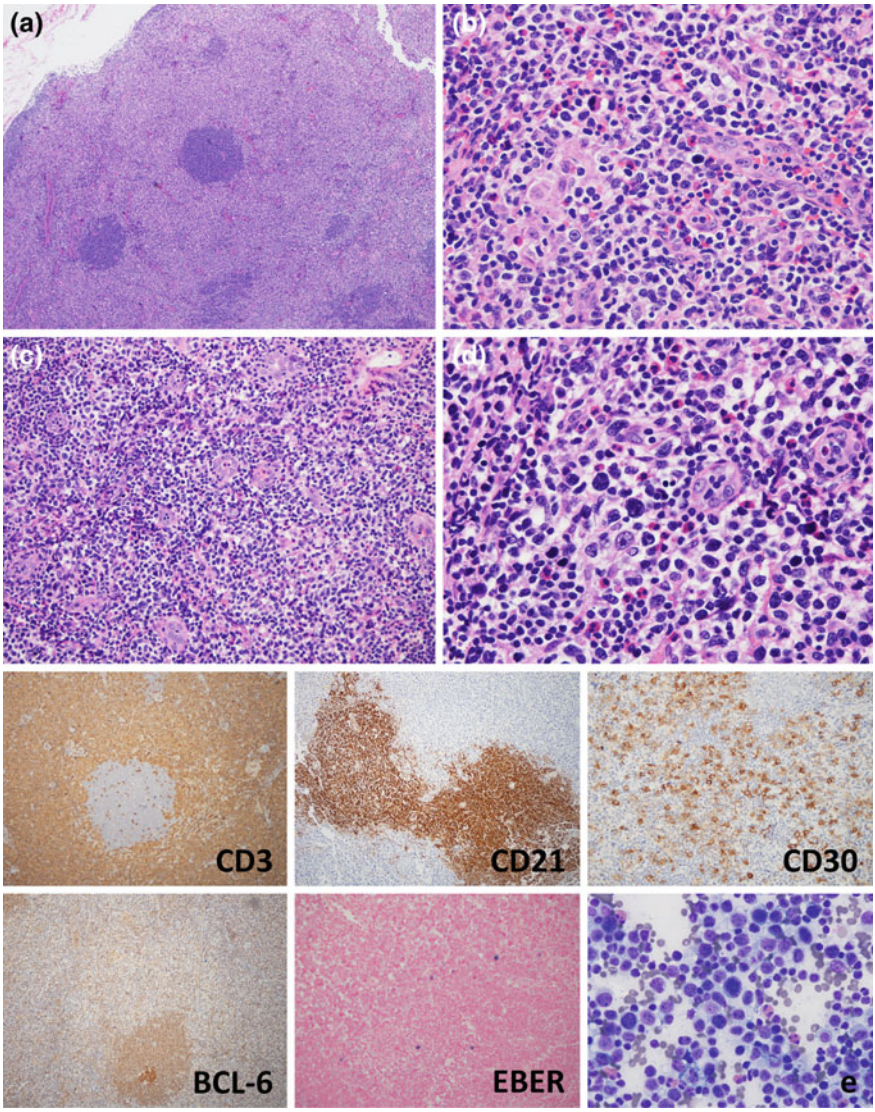

Fig. 4 **a**–**d** AITL. There is preservation of residual follicles, and the neoplastic cells have a clear abundant cytoplasm, and there are associated high endothelial venules and focal RS-like cells (**d**). The tumor cells are positive for CD3 and BCL-6. CD21 shows disrupted FDC. CD30 stains numerous immunoblasts (B cells). EBER is positive in scattered lymphoid cells. The touch preparation **e** also shows eosinophilia

The abnormal cells are usually positive for CD3, CD4, CD10, and CD279 (PD-1), a phenotype characteristic of TFH [159, 160, 162]. Strong expression of CD10 and PD-1 in perifollicular lymphocytes can be helpful in the differential

diagnosis with reactive hyperplasia [168, 169]. However, PD-1 is more weakly expressed normally in paracortical T cells, and therefore, only strong intense staining is diagnostically useful. CXCL13 [170], a chemokine involved in B-cell trafficking into the germinal centers, is also expressed in AITL. B-cell markers are positive in the residual follicles and also stain many immunoblasts in the interfollicular areas. The population of immmunoblasts, when extraordinary numerous, can mimic a DLBCL [171]. Expansion of the FDC is better seen with CD21. EBV-positive B cells comprise the most frequently identified atypical B-cell component in AITL and are nearly always present in the background. The EBV+ cells can resemble Hodgkin lymphoma morphologically and immunophenotypically, and a wrong diagnosis could sometimes be made [172, 173]. Some cases can transform into a DLBCL [174]. Rarely, proliferations of TdT+ cells can be seen [175]. TCR gene rearrangement and clonal IGH can also be present.

At a molecular level, *TET2, DNMT3A,* and *IDH2* mutations have been recently reported in AITL [176, 177]. These mutations, however, are not specific and can also be seen in other PTCLs. Lately, a mutation of *RHOA*, which encodes a GTPase, was reported in 68 % of AITL and is associated with TET2 mutations [178, 179]. CGH studies have shown non-specific gains of chr X, 3, 5, 11q13, 13q, and 22q [180].

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

Clinical and Epidemiologic Features

PTCL, NOS encompasses a heterogeneous group of lymphomas, which essentially do not meet the criteria for any of the other subtypes of mature T-cell lymphomas. Using this definition PTCL, unfortunately, represents a diagnosis of exclusion [181]. PCTL can present in nodal and extranodal sites and has a variety of morphologic patterns, some of which are shared by other subtypes of NHLs. In this sense, the use of PTCL, NOS as a 'waste basket' category not only represents a histologic dilemma, but also affects substantially the way the patients are treated and the overall prognosis. Novel approaches, using gene expression arrays, are a promising tool to better define this subgroup of T-cell lymphoproliferative disorders [2, 140, 161, 182]. Interestingly, the WHO has preserved its use as a 'permanent' and not 'provisional' category. Comparison of interobserver agreement has shown a high rate of discordant results for its diagnosis [34, 183, 184].

PTCL, NOS is the most common subtype of PTCL (30–60 % of cases). It is less common in Asia, where EBV-associated PTCLs are more common [185]. It affects primarily adults, with a mean age of 60, and a higher prevalence in males (2:1). Most patients present with lymphadenopathy with or without extranodal extension. Between 40 and 60 % of patients present with stage IV disease [186–188]. Some can have eosinophilia, pruritus, erythroderma, and rarely hemophagocytosis [163, 189, 190].

Histopathology, Immunophenotypic, and Molecular Features

By definition, the morphology is heterogeneous [53]. In most circumstances, the neoplastic cells are medium to large, and some cases can have a small cell component [2, 5]. In those cases with resemblance to AITL (Follicular variant, see below), cells with clear cytoplasm are present. The presence of Hodgkin-like cells (RS-like) has been documented (particularly in the lymphoepithelial variant) [173, 191]. The background cells include eosinophils, plasma cells, histiocytes, and prominent vessels (Fig. 5). The nodal involvement shows effacement of the architecture with a follicular or parafollicular patterns. Prominent sinusoidal involvement can be seen in those with features resembling ALCL. The distinction between ALCL and PTCL, NOS is important, as the former appears to have a better prognosis and a better outcome after bone marrow transplantation [144, 192]. The WHO recognizes three specific variants: lymphoepithelial, follicular, and T-zone [181]. Lennert lymphoma (lymphoepithelial variant, LE) [191, 193, 194] usually shows scattered neoplastic cells (small to medium in size) with an abundance of epithelioid histiocytes with a granulomatous appearance. Admixed RS-like cells are present [173, 191]. Eosinophils and plasma cells in the background are seen. In the follicular variant [2, 4, 170, 172], there are expanded follicles with a population of neoplastic interfollicular cells of medium size and with clear cytoplasm. FDCs can be present. The T-zone variant [186] shows residual non-neoplastic follicles and an extensive perifollicular neoplastic population of cells.

The immunophenotype shows aberrant loss of 1 or more T-cell antigens, most commonly CD3, CD5, or CD7. The majority of the cases are CD4+, but some can be CD8+, particularly the LE variant [191, 193]. In addition, some cases can be double positive or double negative for CD4 and CD8. The majority of cases have a TCRαβ phenotype, but some are negative, and a small subset is TCRγδ [195]. Cytotoxic markers can be expressed in PTCL, NOS. Some cases express CD30, and a minority CD15 [196]. Cases with significant expression of CD30 should be distinguished from ALK− ALCL. Gene expression profiles have proven beneficial in this situation [197]. Aberrant B-cell antigenic expression can be seen, including multiple B-cell markers (CD20, CD79a, and CD19) [198–200]. The follicular variant shows markers of follicle center T-cell phenotype (T_{FH}): CD10, BCL-6, CXCL13, and/or PD1. The distinction between AITL and the PCTL with T-helper phenotype could be very difficult, and overlap between the two, by gene expression analysis, has been seen [148]. However, this PTCL subtype appears to have a better prognosis and is of extraordinary importance to recognize. It has been proposed more recently the use of at least 3 T-helper markers (e.g., CD10, BCL-6, PD-1, CXCL13) on the evaluation of a new diagnosis of T-cell lymphoma [2]. EBV positivity can be seen in some cases of PTCL, NOS, but diffuse positivity is certainly uncommon [201, 202].

Molecular studies have shown non-specific alterations with some exceptions: Some cases of the follicular variant show a t(5;9) translocation fusing the tyrosine kinase genes *ITK* and *SYK* [2, 4, 6, 203, 204]. Rare cases have shown a t(6;14) translocation with involvement of the *IRF4* and *TRA* genes [152]. Those cases show

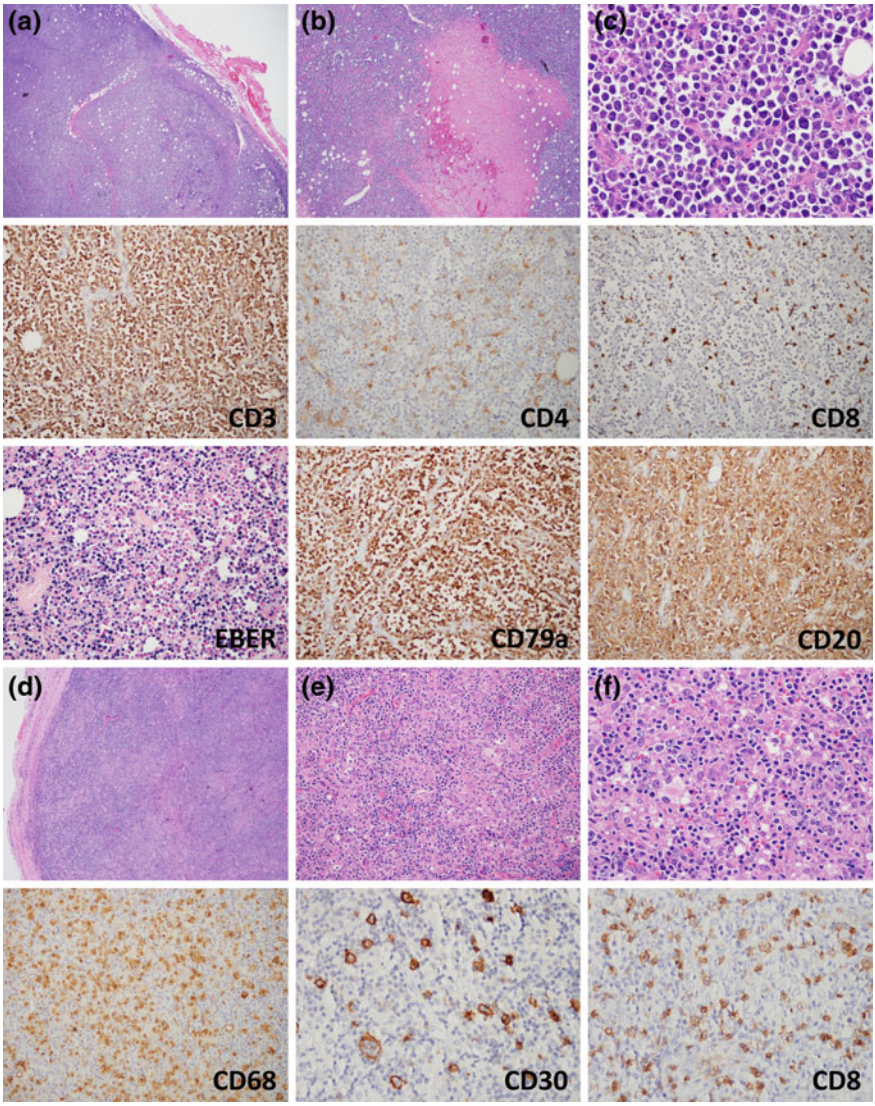

Fig. 5 PTCL, NOS. **a–c** there is a diffuse proliferation of medium-to-large cells which form vague alveolar structures. In this case, the tumor shows diffuse expression of CD3 and EBER, with aberrant coexpression of CD79a and CD20. Both CD4 and CD8 are negative in the tumor cells. **d–f** lymphoepithelial variant (Lennert lymphoma). A rich histiocytic background and granulomatous-like areas are seen. Frequent RS-like cells are present. The immunophenotype of this variant is typically CD8 positive, and CD30 stains the RS-like cells. CD68 shows numerous histiocytes in the background

MUM1 expression and a cytotoxic phenotype in association with diffuse bone marrow infiltration. Amplification of the *CDK6* gene is seen in 23 % of cases [205]. *TET2* mutations, typical or AITL, are present in 20 % of cases and cannot be used to distinguish between the two [6, 177, 206, 207]. Similarly, more recently mutations of the RHOA GTPase appear to be very frequent among them [208]. *BCL-3* rearrangements are also rare [209]. Certain micro-RNA (miRNA) profiles can also help to distinguish among certain subtypes of PCTLs [210]. Rearrangements of the *TP63* gene, present in only 5 % of cases of PTCL, NOS, predict a worse prognosis [211]. Cases with overlap features with AITL can show *IDH2* mutations [197].

1.3 Extranodal T-Cell Lymphomas, Non-Cutaneous

1.3.1 Hepatosplenic T-Cell Lymphoma (HTCL)

Clinical and Epidemiologic Features

HTCL accounts for only 3 % of all T-cell lymphomas in the United States. It affects the liver and spleen and is characterized by a γδ phenotype [212]. Normally, this population of lymphocytes accounts for only 1–3 % of the peripheral blood lymphoid cells. The γδ cells represent part of a repertoire linked to innate or non-specific immune system. The neoplastic T cells in HTCL are similar to the functionally immature cytotoxic γδ T cells observed in the setting of solid organ transplantation [213–216]. The potential role of an immunosuppressed state in the pathophysiology of the disease is also supported by an increased incidence of HTCL in patients with inflammatory bowel disease and rheumatoid arthritis who have undergone treatment with tumor necrosis factor (TNF) blockers and thiopurine [214, 217–219]. HTCL usually presents in young individuals (mean age of 34) with fever, weight loss, splenomegaly and, in some cases, jaundice. Hemophagocytosis can also be seen [220, 221]. Hepatomegaly is seen in 50 % of cases. Laboratory findings include elevation of liver enzymes, LDH, anemia, and thrombocytopenia [57, 212, 214, 222, 223].

Histopathology, Immunophenotypic, and Molecular Features

The neoplastic cells infiltrate the red pulp of the spleen, with a reduction or complete atrophy of the white pulp [224]. In the liver, sinusoidal infiltration by neoplastic cells can be observed in virtually all cases [53]. The portal triads are relatively spared [225]. Perisinusoidal fibrosis without hepatocyte involvement has been described. Lymphadenopathy is almost never present, at least at the time of first presentation, with only a few cases that demonstrated infiltrated lymph nodes by medium-sized lymphoma cells. Bone marrow infiltration is virtually always present (Fig. 6). The infiltration is better appreciated with the use of immunostains. Throughout the course of the disease, a change in the pattern of bone marrow infiltration as well as cell morphology can be observed. With progression, the distribution changes from sinusoidal to increasingly interstitial, and the neoplastic cells become larger and blast-like [226, 227].

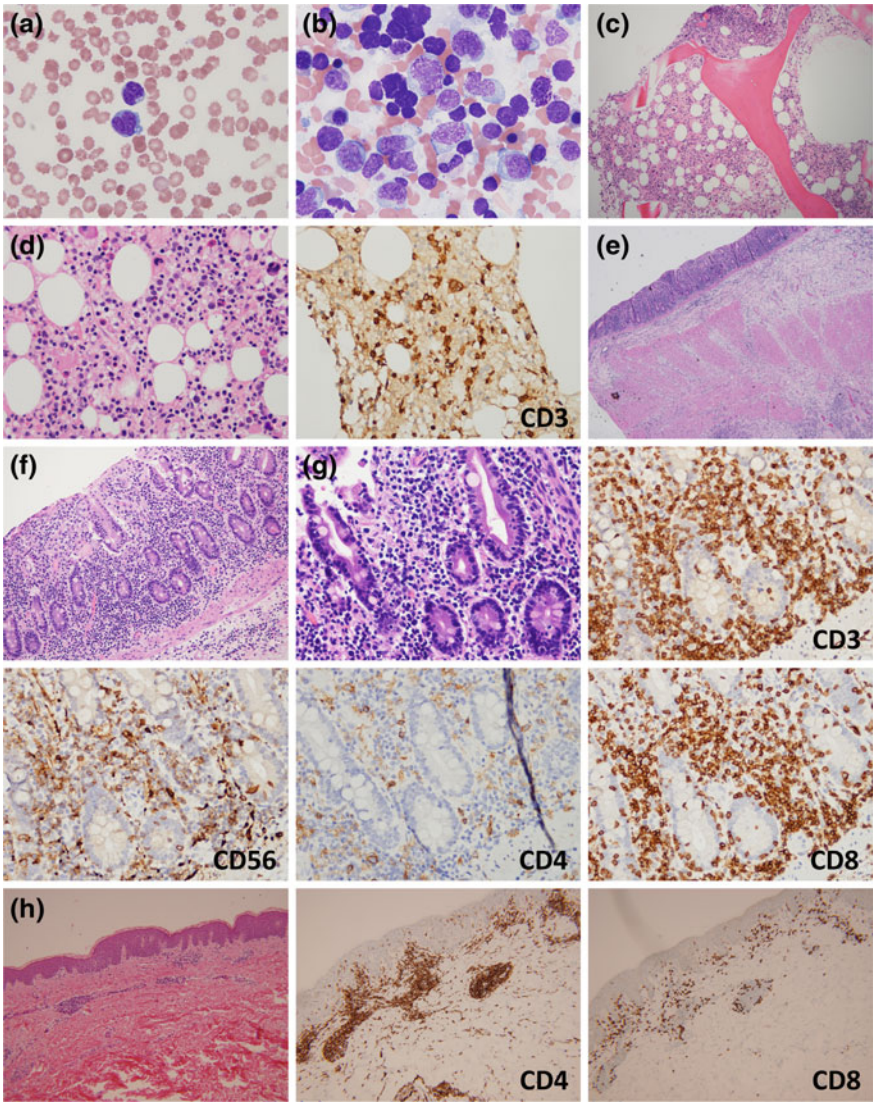

Fig. 6 **a** (PBL)–**b** (aspirate) of HSTCL. In the evolution of the disease, blast-like forms are appreciated. **c**, **d** show bone marrow involvement with a sinusoidal pattern, shown better with the CD3 immunostain. **e** and **f** EATL-2. There is a monotonous infiltrate of medium-to-large cells in the jejunum. The malignant cells are positive for CD3, CD56, and CD8, while negative for CD4. 6 h—SS with cutaneous involvement. Often the histologic findings are very deceptive, with only a mild perivascular lymphocytic infiltrate. The CD4:CD8 ratio is markedly increased

Immunophenotypic studies reveal a γδ phenotype (which can be demonstrated by flow cytometry or the use of BF1 or γδ-antibodies). Rare cases show an αβ-phenotype [228, 229]. Most cases express CD3 and are positive for CD8 and CD56.

The malignant cells express TIA-1 and granzyme M, but negative for perforin and granzyme B. These features are indicative of a non-activated cytotoxic phenotype [2, 6, 57, 212, 214, 225]. KIRs are often expressed [230]. Isochromosome 7q seems to be the primary and consistent chromosomal abnormality detected in most patients with the disease [231–234]. The presence of i(7)(q10) in HTCL seems to be independent of the immunophenotype of the malignant cells. One study revealed the tendency of HTCL to multiply the i(7)(q10) chromosome during evolution and progression of the disease [234]. Clonal ring chromosome 7 formation has been described in HTCL as well, in which the ring chromosome often exhibits 7q amplification with 7p deletion, which results in a i(7)(q10)- equivalent genetic situation [235, 236]. Trisomy 8 is another frequently observed genetic abnormality in HTCL. Other, less common, genetic mutations are loss of chromosome 21, Y and deletion of chromosome 11q14, t(7;14)(q34;q13), and deletion of chromosome 2q23;q37 [226, 227].

1.3.2 Enteropathy-Associated T-Cell Lymphoma (EATL)

Clinical and Epidemiologic Features

Enteropathy-Associated T-cell Lymphoma (EATL) is an intestinal T-cell lymphoma that occurs most commonly in the jejunum or ileum and is particularly frequent in Northern Europe, where the prevalence of celiac disease (CD) is high [237–241]. Rare cases present in the duodenum, stomach, or colon [242, 243]. It has seen in approximately 2–3 % of patients with CD [239]. There are two separate subtypes: EATL-1 and EATL-2. EATL-1 is associated with CD and EATL-2 is not. Clinically, EATL presents at a mean age of 57. In 32 % of cases, EATL was diagnosed during an emergency surgery for small bowel obstruction or peritonitis, due to a perforated tumor. The remaining is diagnosed due to pain, weight loss, or fever [240]. Rare cases present with a hemophagocytic syndrome [244, 245]. In 27 % of cases, CD and EATL are diagnosed simultaneously. The interval between the development of CD and EATL is approximately 50 months. The lymphoma is localized (57 %) or diffuse (43 %). Grossly, the typical features include ulcers (29.7 %), or infiltration and induration of the intestinal wall with out without nodules (48.6 %) [240]. Involvement of extra-intestinal sites such as lymph nodes [246], skin [247], and CNS [248] has been described.

Histopathology, Immunophenotypic, and Molecular Features

In EATL-1, there is an infiltration of lymphoma cells with pleomorphic appearance (medium-to-large lymphoid cells), mixed with reactive small lymphocytes, plasma cells, histiocytes, and eosinophils. The mucosa adjacent to the tumor shows enteropathic changes of CD, including an increase in intraepithelial lymphocytes and villous blunting [237, 238, 240, 249]. EATL-2 shows a monomorphous population of large cells with hyperchromatic nuclei and pale cytoplasm (Fig. 6). It often lacks the inflammatory background seen in EATL-1 and frequently is accompanied by necrosis [237, 241, 250]. Some very early cases may not present with a mass and

show an in situ (intraepithelial component) only ('in situ' EATL). A histologic variant of EATL with anaplastic morphology has also been described.

In EATL-1, the neoplastic T cells are positive for CD3, CD7, and CD103, but are typically negative for CD4, CD8, and CD5, and show variable reactivity with CD30 and TCRαβ [237, 239, 240, 251]. They may also co-express cytotoxic markers such as granzyme B, perforin, and/or TIA1. The adjacent intraepithelial lymphocytes may also express abnormal immunophenotype with loss of CD5, CD4, and CD8 expression. In EATL-2, the malignant cells express CD3, CD56, CD8, and TCRαβ. Molecular studies show (in both EATL-1 and EATL-2) 9q31.3-qter amplifications or 16q12.1 deletions [5, 238, 249, 252]. Gains in 1q32.2-q41 and 5q34-q35.2 occur in EATL-1, while amplifications of *MYC* are present in EATL-2 [250, 253, 254]. More recently, Perry et al. [255] have proposed the term indolent T-cell lymphoproliferative disease of the gastrointestinal tract, to define a rare group of lesions with an immunophenotype similar to EATL. This group of patients had no history of enteropathy and had a very indolent clinical course, without the need for chemotherapy.

1.4 Extranodal T-Cell Lymphomas, Cutaneous

1.4.1 Mycosis Fungoides

Clinical and Epidemiologic Features

MF is the most common type of cutaneous T-cell lymphoma, accounting for 50 % of all primary cutaneous lymphomas [99, 256]. Its annual incidence has been estimated to 6 or 7 cases per 1 million persons. MF occurs more commonly in adults, although any age group can be affected. The male-to-female ratio is 2:1 [257]. Classic MF is a disease that progresses slowly over years and sometimes decades, presenting with well defined, often pruritic erythematous patches distributed in non-sun-exposed 'bathing suit' areas, including the breasts, buttocks, lower trunk, and groin. These patches may evolve to infiltrative plaques and tumors, and all 3 lesion types can be seen concomitantly. Hypopigmented lesions are a rare presentation of MF, most often seen in children, adolescents, and dark-skinned individuals [258–261]. Approximately 30 % of patients present with skin tumors or erythroderma at disease onset [101, 262]. Extracutaneous dissemination occurs in advanced stages and may involve lymph nodes [263], liver [264, 265], spleen [266, 267], lung [268], and blood. However, bone marrow involvement is rare [269].

Histopathology, Immunophenotypic, and Molecular Features

MF is an epidermotropic T-cell lymphoproliferative disorder composed of small-to-intermediate atypical lymphocytes with enlarged hyperchromatic, cerebriform nuclei, and clear cytoplasm. The morphology varies with the clinical stage of disease (Fig. 7) [99, 101, 104, 120, 257, 262]. The early patch of skin shows lichenoid atypical lymphoid infiltrate colonizing the basal layer in a singly or linear

fashion, whereas plaque stage shows more prominent epidermotropism. Pautrier microabscesses, consisting of small intraepidermal aggregates of atypical lymphocytes and Langerhans cells, are seen in only 25 % of cases. With progression from patch/plaque stages to tumor stage, more diffuse involvement of papillary dermis and increase in number and size of neoplastic T-cell lymphoid infiltrates occurs. Epidermotropism may be lost. The following features are not typically seen in MF: marked spongiosis, vacuolar change, keratinocyte necrosis, or numerous eosinophils and/or neutrophils. Histologic transformation, defined as the presence of large T cells in more than 25 % of the total lymphoid infiltrate or forming microscopic nodules, is an adverse finding. Some histologic variants are summarized in Table 2 and illustrated in Fig. 7 [99, 265, 270–278].

Immunophenotypically, the neoplastic T cells in MF are usually CD4 mature T cells with expression of CD2, CD3, TCRB, and CD5. Loss of one or more T-cell antigens (CD7, most common) is frequent in all stages [99, 101, 104, 120, 257, 262, 272]. CD8− positive MF has been seen more commonly in pediatric MF [258, 261] and with pagetoid reticulosis [274]. The clinical behavior of CD8 phenotype MF is similar to that of CD4 phenotype. These large cells may be CD30− or CD30+. Prognosis appears to be better in LCT with CD30 expression [279]. MF may coexist with CD30+ T-cell lymphoproliferative disorders such as cutaneous ALCL and lymphomatoid papulosis (LyP) [280, 281]. It is important to distinguish concurrent MF with cutaneous ALCL with transformed MF because of their prognosis and therapeutic implications are different. MF is a clonal disorder of memory T cells. Clonal T-cell gene rearrangement has been seen in variable proportion of cases by molecular studies [282]. However, clonal T cells are frequently found in non-neoplastic and inflammatory skin conditions [283–287], thus diagnosis of MF cannot be made on the basis of molecular study alone and requires clinical–pathological correlation. The diagnosis of early MF can be challenging because not all pathologic findings are present or because of overlapping findings with other reactive dermatoses. At a molecular level, MF lacks CCR7/L-selectin and CD27 but strongly expresses CCR4 and CLA, a phenotype suggestive of skin resident effector memory T cells [288]. This phenotype is different from SS where the T cells show a central memory pattern. Expression with CCR7 also correlates with loss of epidermotropism and subcutaneous extension [289]. aCGH studies have shown some numerical alterations including recurrent loss of 19, 7p22.1-p22.3, 7q11.1-q11.23, 9q34.12, 12q24.31, and 16q22.3-q23.1, and gain of 8q22.3-q23.1 and 21q22.12 [290]. Limited micro-RNA (miRNA) studies have shown a signature of specific miRNA when comparing MF against inflammatory skin disorders [291, 292].

1.4.2 Subcutaneous Panniculitis-like T-Cell Lymphoma (SPTCL)

Clinical and Epidemiologic Features

SPTCL is a primary cutaneous T-cell lymphoma with preferential involvement of the subcutaneous tissue and is now a distinct category in the WHO. The cases, originally included under this category with a TCRγδ phenotype, are now included

Table 2 Histological variants of mycosis fungoides

	Morphology	Histology	Immunophenotype	Prognosis
Mycosis fungoides	Clinical three stages: patches, plaques and tumor stages	Superficial band such as atypical small-to-medium-sized, indented nuclei (cerebriform) lymphoid infiltrate, at dermoepidermal junction. Epidermotropism with little spongiosis and Pautrier microabscesses	CD3+, CD4+, CD8 −, with loss of pan-T-cell antigen (CD2, CD7, CD5)	Depends on clinical stage; type and extent of cutaneous lesion, presence of extracutaneous disease and/or lymph node involvement
Folliculotropic MF	Follicular papules, acneiform lesions and indurated plaques	Atypical lymphocytic infiltrate around and within the follicular epithelium and relative sparing of surface epithelium	CD3+, CD4+, CD8 −, CD30+ (variable blast cells)	Worse prognosis than that of patients with classical plaque stage MF
Pagetoid reticulosis (PR)	Solitary psoriasiform or hyperkeratotic patch or plaque	Hyperplastic epidermis with marked infiltration by atypical pagetoid medium-to-large-sized lymphocytes	CD3+, CD4+, CD8 − or CD3+, CD4−, CD8+	Indolent course with potential to frank malignant behavior
Granulomatous slack skin (GSS)	Circumscribed erythematous masses of lax skin (body folds)	Dense granulomatous dermal infiltrate containing atypical T cells, macrophages and multinucleated giant cells	CD3+, CD4+, CD8 −	Indolent clinical course

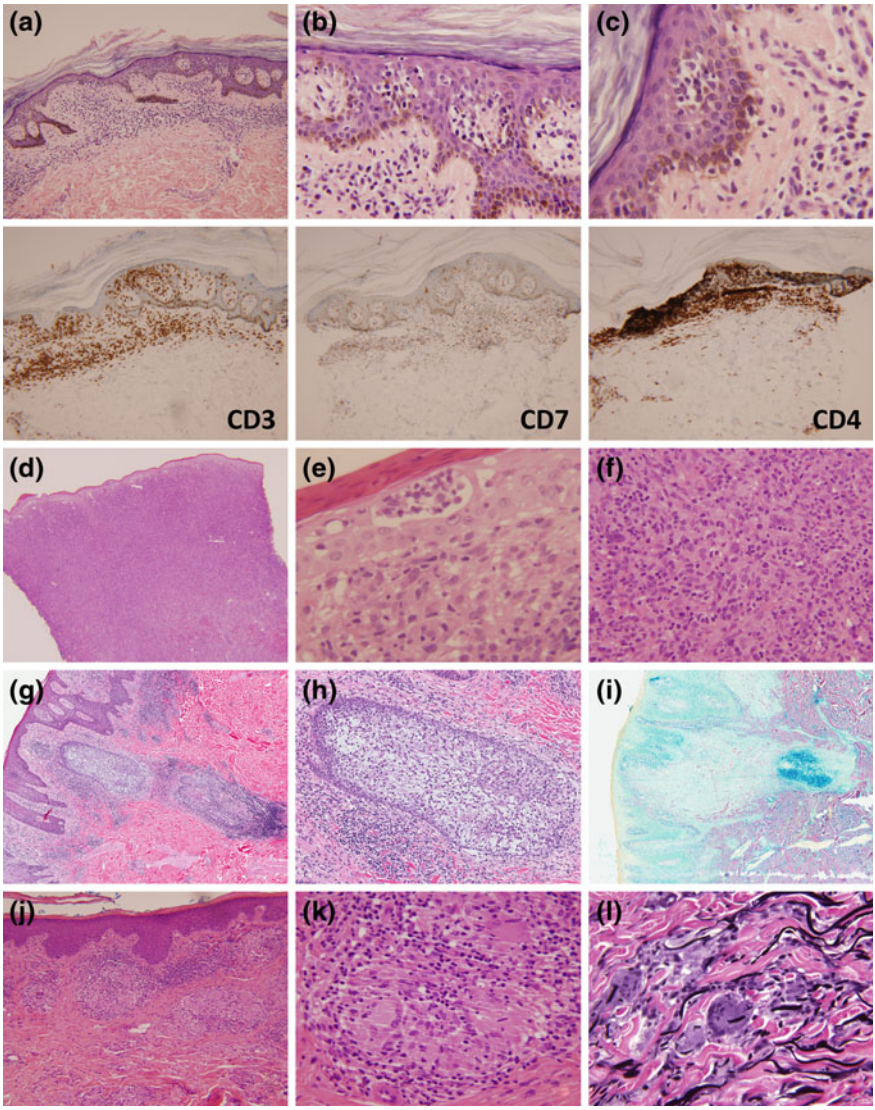

Fig. 7 MF and variants. **a**–**c** Classic variant with epidermotropism, and tagging of lymphocytes along the dermal–epidermal junction. The abnormal T cells are CD3+ , have loss of CD7, and have a CD4+ phenotype. **d**–**f**, Large cell transformation. This is defined by >25 % large cells. The presence of Pautrier microabscesses is seen in **e**. **g** and **h**, folliculotropic variant with associated follicular mucinosis (**i**, colloidal iron). **j**– **k**, Granulomatous variant (granulomatous slack skin) with elastophagocytosis (**l**, elastic stain)

under the provisional category of primary cutaneous γδ-T-cell lymphoma [101, 163, 165, 293–296]. It is more common in younger individuals, and 20 % of cases occur in individuals of <20 years of age [297]. The clinical presentation includes skin

nodules in the extremities and the trunk, but some cases can present in the head and neck region. Ulceration is usually rare. Extracutaneous involvement is also uncommon [298]. Those cases with hemophagocytosis (17 %) have a worse prognosis [294, 296, 299].

Histopathology, Immunophenotypic, and Molecular Features

There is a dense lymphoid infiltrate of small-, medium-, and large-sized lymphocytes, preferentially in the subcutaneous tissue, within the fat lobule. Extension in the dermis is usually seen. The epidermis must be spared. The atypical lymphocytes are hyperchromatic, have angulated nuclei, and clear cytoplasm. Admixed inflammatory cells, such as histiocytes, plasma cells, and neutrophils, can be seen [295, 296]. The classic pattern of infiltration shows rimming of the adipocytes by the atypical lymphoid cells (Fig. 8). The immunophenotype shows that the abnormal T cells are CD3+, CD4−, CD8+, and CD56−. In some cases, the T cells are CD4−/CD8−. Invariably they express TCRβ. The tumor cells express the cytotoxic markers TIA-1, perforin and granzyme. Cases with overlap features with lupus panniculitis have been described [300–302]. In those, CD123 has been proposed to be useful (positive in plasmacytoid dendritic cells in lupus) [303]. At a molecular level, CGH revealed large numbers of DNA copy number changes, the most common of which were losses of chromosomes 1pter, 2pter, 10qter, 11qter, 12qter, 16, 19, 20, and 22 and gains of chromosomes 2q and 4q [294, 304].

1.4.3 Cutaneous Anaplastic Large Cell Lymphoma (C-ALCL)

Clinical and Epidemiologic Features

C-ALCL usually has an indolent clinical course and overlaps with the clinicopathologic features with LyP. Most patients are adults, and usually 50–60 years of age [305, 306]. It is rare in children, but occasionally reported [307]. Clinically presents as a solitary tumor or nodule, often ulcerated and located on the face, extremities, or less frequently the trunk. Multifocality is seen in 20 % of cases. Spontaneous regression occurs in 25 % of cases [308, 309]. Mucosal CD30 + lymphoid proliferations with significant overlap features to C-ALCL have been reported recently [310].

Histopathology, Immunophenotypic, and Molecular Features

The histology of the lesion includes cohesive sheets of large anaplastic cells, with indented and irregular nuclei, and abundant cytoplasm, similar to other systemic ALCLs. In 20 % of cases, a variant morphologic appearance is seen (a rare small cell variant has been reported). The infiltrate extends from the dermis into the subcutis [280, 308, 311, 312]. Admixed acute inflammatory cells can be very prominent (giving rise to pyogenic- and eosinophilic-rich cell variants). In 25–30 % of cases, there is pseudoepitheliomatous hyperplasia of the skin. The pathologic overlap between C-CLCL, LyP and large cell transformation in MF heralds the absolute need of a good clinical history to distinguish between the different lesions

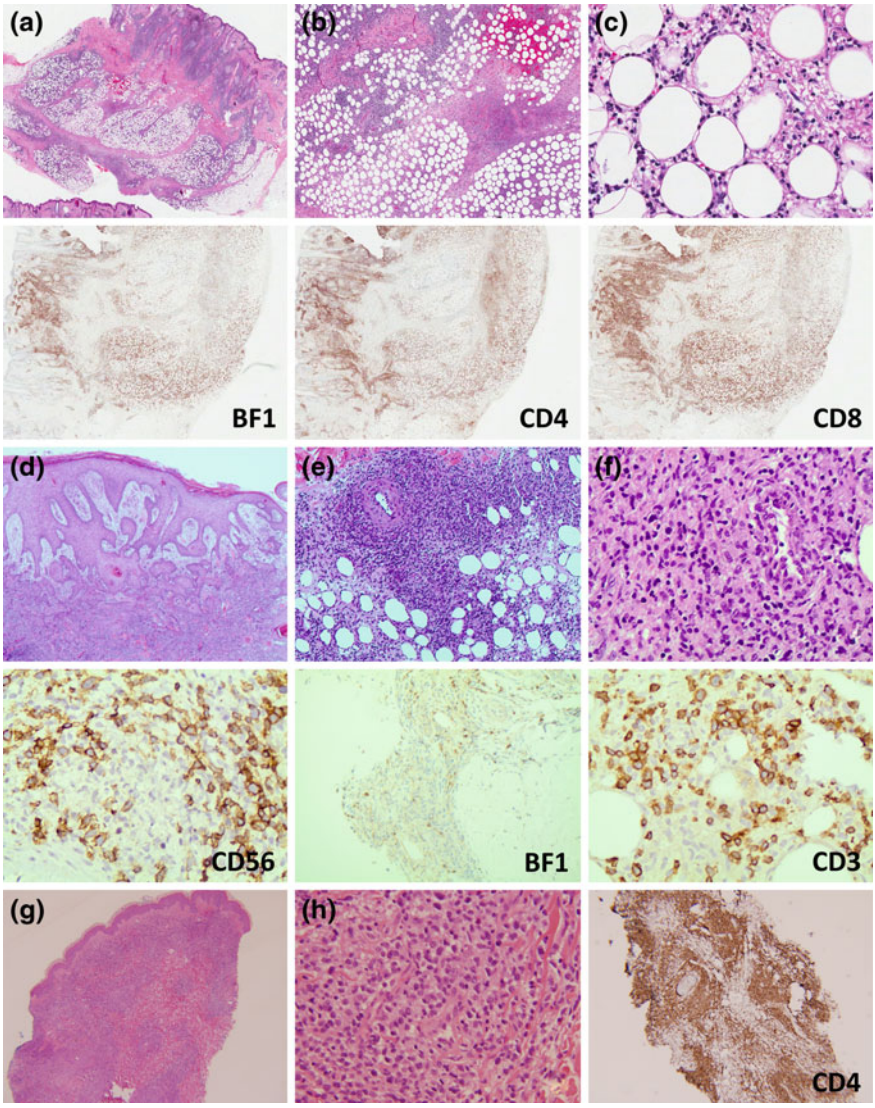

Fig. 8 Cutaneous T-cell lymphomas, rare forms. **a–c** SPTCL. There is a classic lobular panniculitis with necrosis and rimming of adipocytes by the abnormal cells. BF1 is positive indicating a TCR-αβ receptor. The CD4:CD8 ratio is inverted as the tumor cells are CD8 positive. **d–f** PCGDTCL. Pseudoepitheliomatous hyperplasia is frequently observed (**d**). The tumor also infiltrates the fat, and angioinvasion is frequent (**f**). The tumor cells are CD56+ and CD3+. BF1 is predominantly negative, indicating a γδ-receptor. **g–h**, SMPTCL. There is sparing of the epidermis and a CD4 phenotype

[313]. Some cases can have a marked predominant intravascular distribution [314–316]. All cases show diffuse and strong CD30 expression, variable loss of pan-T-cell antigens and some expression of cytotoxic markers. EMA is expressed in 20–30 % of cases. ALK expression is associated with systemic disease, but rare cases of C-ALK+ ALCL have been published [135]. Variable expression of clusterin and CD56 (12–75 %) is seen. Like LyP, MUM1 is frequently positive.

Loss of TGF-β–induced lymphocyte growth inhibition has been demonstrated in C-ALCL, due to a dominant negative mutation of the TGF-β type II receptor or deletion of the initiating sequence for translation of the type I receptor transcripts; this observation suggests that altered TGF-β/SMAD signaling may play a role in the progression of LyP to ALCL. Recurrent translocations involving multiple myeloma oncogene 1/interferon regulatory factor 4 (*MUM1/IRF4*) (located on 6p25) have been detected by FISH in C-ALCL (57 % of cases tested), rare PTCL, NOS (5 %), and systemic ALK2 ALCL (4 %) [152, 153, 317]. Amplification of *JUNB* (19p13) is reported in 70 % of C- ALCLs, and JUNB protein expression is present in virtually all cases, which might promote tumor cell survival via its upregulation of CD30 and thereby NF-kB activation [114, 115]. Numerous other alterations have been described on aCGH. Differences in miRNA have been shown to distinguish it from MF [318]. CALCL exhibits gain of 7q31 and loss on 6q16-6q21 and 13q34, each affecting 45 % of the patients, and has a distinct signature that distinguishes it from MF and SS [122, 319].

2 Concluding Remarks

Our understanding of the diversity of PTCLs has evolved substantially over the past 20 years and is reflected in the evolution of classification schemes. Numerous categories in the WHO still remain at a provisional stage, and some include very complex and heterogeneous disorders, for which we expect subclassifications to arise. The accuracy in the diagnosis of PTCL among different experts has been previously studied: The International T-cell Lymphoma Project showed an overall rate of 81 %. The reproducibility for the diagnosis of ALK+ ALCL was 91 %, but was much lower for PTCL, NOS (81 %) and AITL (75 %) [145]. More recently, the accuracy has increased to 92 % on a study from Hsi et al. [184]. Gene expression profiling (GEP) has been performed to improve the diagnosis of PTCL and to better understand its pathobiology. To this respect, a study by Iqbal et al. [197] showed that by using this methodology 14 % of cases previously diagnosed as PCTL were reclassified as AITL. In the same study, 11 % of PTCL were reclassified as ALK− ALCL. Interestingly, those cases that were categorized as ALK− ALCL had a worse prognosis compared to PTCL, NOS. A study by Piccaluga et al. [320] has also shown that GEP improves classifications of AITL and ALCL: In their study, the traditional morphologic and immunophenotypic approach failed to provide significance in survival between ALCL and PTCL, NOS but, with the use of GEP, a statistical significance in survival was achieved. Two genetic subgroups emerged in

the PTCL, NOS groups: a *GATA3* high subgroup with enrichment of proliferation signatures (*MYC,* mTOR, β-catenin) and a *TBX21* subgroup, with activation of pathways linked to IFN-γ and NFkB, and better prognosis. Ultimately, not only will molecular classification improve diagnostic accuracy, but it may lead to the development of a targeted therapy approach with drugs directed to specific pathways: For example, AITL may benefit from FDA-approved drugs that target the NF-κβ pathway including bortezomib or carfilzomib or specific inhibitors against *IDH2* mutation currently in development. ALK− ALCL patients may benefit from drugs that target mitotic cells (e.g., aurora kinase inhibitors) in combination with drugs that target the PI3-kinase/AKT pathway. Similarly, a subset of patients in the GATA3 subgroup may benefit from drugs that target the mTOR (e.g., rapamycin, temsirolimus) pathway [182]. It is more than likely that the next generation of classifications will incorporate these types of approaches for diagnostic purposes and will allow for a better understanding of the pathobiology of these diseases.

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