Chapter 4
Pathology

Koichi Ohshima and Hiroaki Miyoshi

4.1 Neoplastic Lesions

4.1.1 Sites of Involvement

Most Adult T-cell leukemia/lymphoma (ATL) patients present with widespread lymph node involvement as well as peripheral blood. The fact that the concentration of neoplastic cells in a peripheral blood sample does not correlate with the degree of bone marrow involvement suggests that circulating neoplastic cells are recruited from other organs such as the skin and lymph nodes, and indeed, the skin is the most common extralymphatic site of involvement (>50% of patients with ATL) [7]. Other clinically relevant extranodal sites of involvement associated with morbidity include the lungs, liver, spleen, gastrointestinal tract, and central nervous system [8] (Table 4.1).

4.1.2 Clinical Features: Peripheral Blood

Four clinical subtypes of ATL have been identified: acute, lymphomatous, chronic, and smoldering (Table 4.2) [9]. Because most patients have stage IV disease at presentation, the Ann Arbor staging system is not prognostically useful. The most common subtypes, acute ATL, is characterized by a leukemic phase, often with a markedly elevated white blood cell count, skin rash, and generalized lymphadenopathy. The leukemic cells are medium- to large-sized lymphoid cells with

K. Ohshima (✉) • H. Miyoshi
Department of Pathology, School of Medicine, Kurume University, Asahimati 67, Kurume 830-0011, Japan
e-mail: ohshima_kouichi@med.kurume-u.ac.jp

T. Watanabe, T. Fukushima (eds.), *Adult T-cell Leukemia/Lymphoma*,
DOI 10.1007/978-4-431-56523-9_4

Table 4.1 Human T-cell leukemia virus type I (HTLV-1)-related disease

Neoplastic disorders	**Reactive disorders**
Peripheral blood (leukemia)	Confirmed
Smoldering type	HTLV-I-associated myelopathy (HAM)
Chronic type	HTLV-I-associated uveitis
Acute type	Not confirmed
Lymph node (Lymphoma)	HTLV-I-associated lymphadenitis
Hodgkin's-like type	HTLV-I-associated bronchopneumopathy (HAB)
Pleomorphic small-cell type	HTLV-I-associated arthropathy (HAAP)
Pleomorphic (medium- and large-cell) type	HTLV-I-associated nephropathy
Anaplastic large-cell type	Infective dermatitis
Skin	Polymyositis
Erythema	Sjögren syndrome
Papule	Autoimmune thyroiditis
Nodule	Polyneuropathy
Tumor	**Immunodeficiency association**
Gastrointestinal tract	Strongyloidiasis (gastrointestinal tract)
Erosion	Varicella zoster (skin)
Ulceration	Crusted scabies (skin)
Tumor	Opportunistic lung infection
Liver	*Pneumocystis carinii*
Portal or sinus infiltration	Cytomegalovirus
Bone marrow	Aspergillus fumigatus
Infiltration with or without fibrosis	*Candida albicans*
Lung	*Cryptococcus neoformans*
Interstitial infiltration	Carcinoma (not confirmed)

Modified from Ref. [64]

Table 4.2 Diagnostic criteria for clinical subtypes of ATL

	Smoldering	Chronic	Acute
Lymphocytosis	No	Increased	Increased
Blood abnormal lymphocytes	>5%	Increased	Increased
LDH	Normal	Slight increased	Increased
Ca	Normal	Normal	Variable
Skin rash	Erythema, papules	Variable	Variable
Lymphadenopathy	No	Mild	Variable
Hepatosplenomegaly	No	Mild	Variable
Bone marrow infiltration	No	No	Variable

Modified from Ref. [9]

irregular nuclei and basophilic cytoplasm. Characteristic ATL cells have been described as "flower cells," with many nuclear convolutions and lobules (Fig. 4.1). Patients with ATL usually have hepatosplenomegaly, constitutional symptoms, and elevated lactate dehydrogenase levels. Hypercalcemia, with or

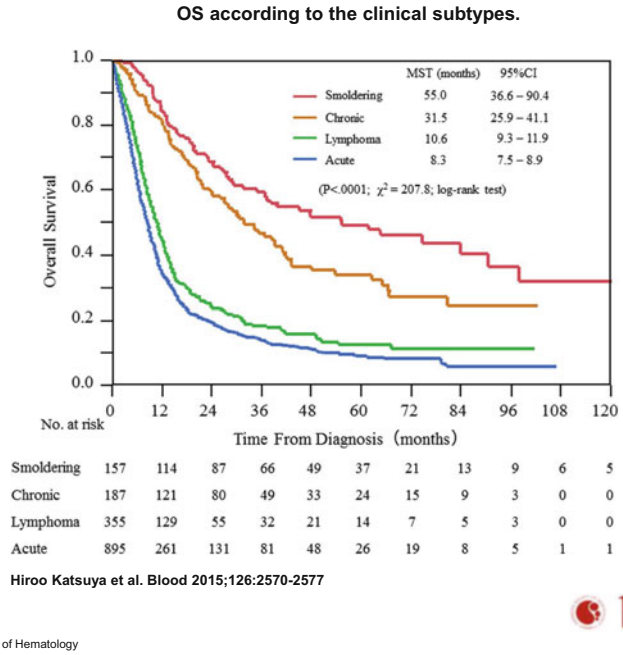

Fig. 4.1 Survival of patients with ATL subtypes. Acute and lymphomatous forms have an aggressive clinical course, whereas longer survival is seen in patients with chronic or smoldering disease (Adapted from Ref. [9]). In peripheral blood of acute ATL, the leukemic cells are medium-sized to large lymphoid cells with irregular nuclei and basophilic cytoplasm. The characteristic ATL cells have been described as "flower cells" because of their many nuclear convolutions and lobules (**a**). ATL cells in the chronic variant are generally small with slight nuclear abnormalities, such as notching, indentation, and convolution (**b**)

without lytic bone lesions, is a common feature, while leukocytosis and eosinophilia are common complications [10].

The lymphomatous variant is characterized by prominent lymphadenopathy. However, there is no peripheral blood (PB) involvement.

The chronic subtype is associated with skin lesions, most commonly exfoliative. While absolute lymphocytosis may be present, atypical lymphocytes are not numerous in the blood. ATL cells of the chronic subtype are generally small with slightly abnormal notched, indented, and convoluted nuclei (Fig. 4.1). Hypercalcemia is absent. Although patients may have hepatosplenomegaly, the clinical course is generally indolent; the median survival is about 2 years [9].

In patients with the smoldering subtype, the white blood cell count is normal, with >5% circulating neoplastic cells. ATL cells are generally small with a normal appearance of small lymphocyte. Patients frequently have skin or pulmonary lesions and do not have hypercalcemia. Progression from the chronic or smoldering to the acute subtype occurs in 25% of cases, but usually after a long period of time (Fig. 4.1) [9].

4.1.3 Lymph Node Lesions

Histopathological examination of HTLV-I-involved lymph nodes usually, although not uniformly, finds lymph nodes with a typical pleomorphic appearance. In addition to the lymph nodes of patients with overt ATL, the lymph nodes of some patients with pre-ATL show a Hodgkin disease-like morphology. The lymph nodes of carriers without ATL manifest features of lymphadenitis [11–13].

4.1.3.1 Lymphomatous Lesions

4.1.3.1.1 Pleomorphic (Medium- and Large-Cell) Type

The medium and large tumor cells vary in size and show obvious nuclear irregularities. Giant cells with cerebriform, Reed-Sternberg-like or bizarre nuclei are frequently seen in lymph nodes (Fig. 4.2a). This type is the typical nodal lesion of ATL.

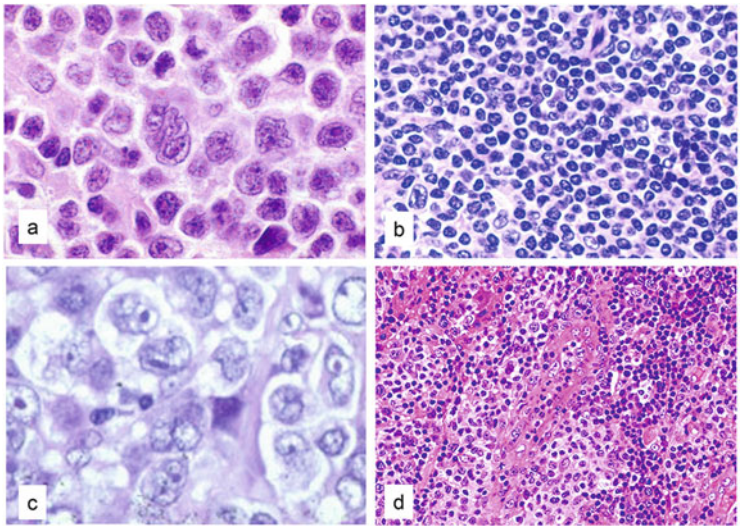

Fig. 4.2 Histology of HTLV-I associated lymph nodes. (**a**) The pleomorphic (medium-sized and large-cell) type shows a diffuse proliferation of atypical medium-sized to large lymphoid cells with irregular nuclei, intermingled with cerebriform giant cells (*center*). (**b**) The lymph nodes of the pleomorphic small-cell type show a diffuse proliferation of atypical medium-sized to small lymphoid cells. (**c**) The anaplastic large-cell type shows a diffuse proliferation of atypical large lymphoid cells with prominent nucleoli. (**d**) AILT-like ATL shows proliferation of high endothelial venules with a variety of infiltrating inflammatory cells

4.1.3.1.2 Pleomorphic Small-Cell Type

Histologically, these tumor cells are as large as or slightly larger than normal lymphocytes in the peripheral circulation (Fig. 4.2b) and show mild nuclear irregularities, with only a few cells displaying mitotic figures. Tumor cells have the phenotype of a peripheral T cell. [13, 14]

4.1.3.1.3 Anaplastic Large-Cell Type

The tumor cells are much larger than the cells of large-cell lymphoma and show a uniform pattern of cell proliferation. Tumor cells with prominent nucleoli and an abundant cytoplasm have been found, and multinucleated giant cells such as Reed-Sternberg cells have also been detected (Fig. 4.2c). Tumor cells express the CD30 antigen and have the phenotype of a peripheral T cell [13, 15].

4.1.3.1.4 AILT-Like ATL

Angioimmunoblastic T-cell lymphoma (AILT) is a rare morphological variant of ATL. Examined lymph nodes have shown proliferation of high endothelial venules and various infiltrating inflammatory cells, including plasma cells and eosinophils (Fig. 4.2d). The lymphoma cells are medium to large in size, with clear cytoplasm [16].

4.1.3.1.5 Immunophenotypes and Genotypes

Tumor cells express T-cell-associated antigens (CD2, CD3, CD5), but usually not CD7. While the cells of most cases are CD4+CD8-, a few are CD4-CD8+ or double positive/negative for CD4 and CD8. CD25, the interleukin-2 receptor alpha subunit, is strongly expressed in nearly all cases. The large transformed cells may be positive for CD30, but are ALK negative [17]. None of the cases appear to have tumor cells that express the cytotoxic molecules T-cell-restricted intracellular antigen and granzyme B. The absence of the expression of these markers is a key consideration in differentiating between ATL and extranodal cytotoxic T-cell lymphoma in HTLV-I-endemic areas. In addition, tumor cells frequently express the CCR4 chemokine receptor and FoxP3, a regulatory T-cell (Treg) marker [18]. The origin of ATL cells has been postulated to be peripheral CD4+ alpha/beta T cells, and it has been suggested that CD4+CD25+FoxP3+ Treg cells are their closest normal counterpart [18] (Fig. 4.3). The follicular T-cell markers CD10, bcl6, and CXCL13 are not expressed by ATL, including AILT-like ATL, tumor cells.

Most ATL cases are characterized by monoclonal integration of HTLV-I proviral DNA, and some by oligoclonal integration, but clonal integration is not present

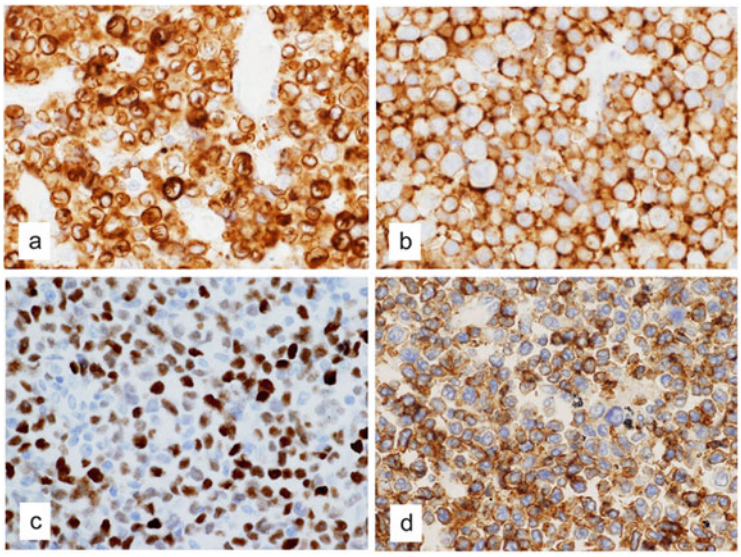

Fig. 4.3 Immunophenotype of ATL. (**a**) ATL cells express T-cell-associated antigen of CD3 (**a**) and CD4 (**b**). (**c**, **d**) ATL cells frequently express FoxP3 of the regulatory T-cell marker (**c**) and CCR4 of the chemokine receptor (**d**)

in carriers [19]. T-cell receptor genes of the α-, β-, γ-, and δ-chains are clonally rearranged in ATL. While a dominant T-cell clone has not been observed in HTLV-I carriers, oligoclonal T-cell expansion can be detected [19].

4.1.3.2 Atypical Lymphomatous and Nonlymphomatous Lesions

4.1.3.2.1 Hodgkin Cell-Like Type

The lymph nodes exhibit a relatively preserved nodal architecture with diffuse infiltration of small- or medium-sized lymphocytes with mild nuclear irregularities. Small aggregated foci or clusters of a few giant cells with irregularly lobulated, highly convoluted, Reed-Sternberg- or Hodgkin cell-like nuclei are scattered throughout the expanded paracortex (Fig. 4.4a). The giant cells occasionally display mitotic features. Immunohistological analysis reveals that proliferating small- to medium-sized lymphocytes possess a peripheral T-cell phenotype of helper/inducer cells (CD1-, CD2+, CD3+, CD4+, CD8-) and that giant cells show a Hodgkin lymphoma phenotype, which reacts with anti-CD30 antibody and/or anti-CD15 and anti-PAX5 antibodies. Analysis of receptor genes has found rearrangement and/or deletion of the T-cell receptor genes Cβ and/or Jγ. Proviral HTLV-I DNA bands have been found, although the bands are weaker than those usually seen in typical ATL, probably because of the small population of integrated HTLV-I lymphocytes. Molecular analysis by single-cell polymerase chain reaction

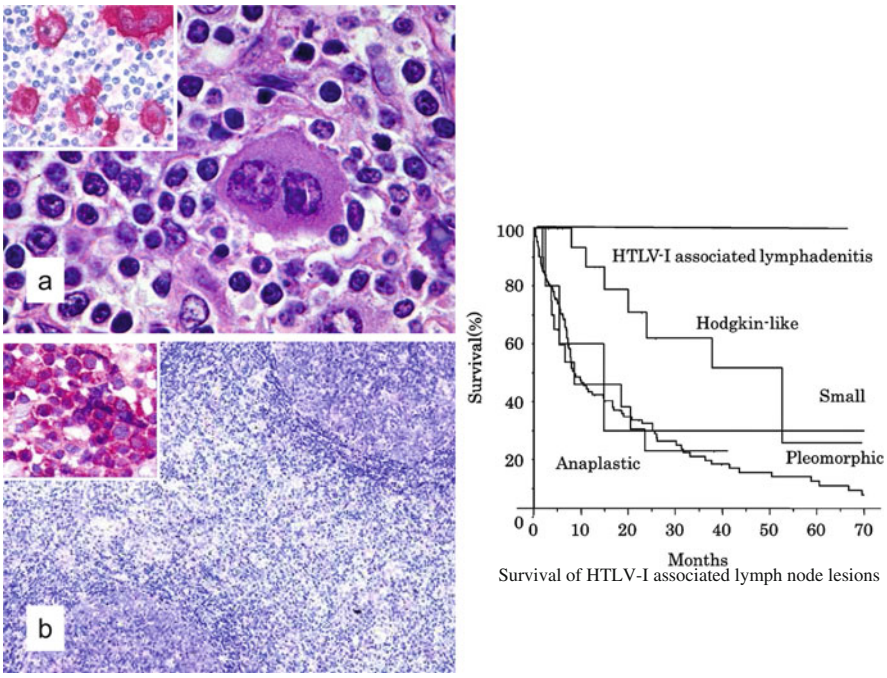

Fig. 4.4 Survival and histology of HTLV-I associated lymph nodes (Adapted from Ref. [13]). (**a**) The lymph nodes of HTLV-I-associated lymphadenitis show an enlarged paracortex with a diffuse infiltration of lymphocytes, which express the CD4 antigen (*inset*). (**b**) The lymph nodes of Hodgkin-like ATL feature Reed-Sternberg-like giant cells, which react with CD30 antibody (*inset*). Survival curve of HTLV-I-associated lymph node lesions. The pleomorphic (medium- and large-cell) and ALCL types are associated with a rapidly deteriorating survival curve, while Hodgkin's type shows a progressive decline in the survival rate. The pleomorphic small-cell type is associated with an initial steep increase in mortality, which reaches a plateau during the middle and late periods of disease progression. In contrast, all cases with lymphadenitis were still alive at the end of the study concerned (Adapted from Ref. [13])

has confirmed that the giant cells are reactive cells that specifically resemble the immature B cell lineage, while the background CD4-positive T cells, which show evidence of clonality, are HTLV-I infected [11, 20].

4.1.3.2.2 Lymphadenitis Type

Histological examination of the lymph nodes of HTLV-I-associated lymphadenitis shows a preserved nodal architecture with small lymphoid follicles, enlargement of the paracortex, and diffuse infiltration by small- or intermediate-sized lymphocytes (Fig. 4.4b), with the latter cells showing slight nuclear irregularities. Immunohistochemically stained sections have shown proliferating small- to intermediate-sized lymphocytes possessing a peripheral helper/inducer T-cell

phenotype (CD1-, CD2+, CD3+, CD4+, CD8-), while no cases have shown rearrangement or deletion of the T-cell receptor genes Cβ and Jγ or rearrangement of the immunoglobulin heavy chain gene (JH). Except for a few cases in which oligoclonal bands were detected, no monoclonal proviral DNA bands have been found. However, these bands were weaker than those of typical ATL cases, probably because of the small population of lymphocytes with integration of HTLV-I proviral DNA [12].

4.1.3.3 Survival Rates

The median survival time (MST) and 2- and 5-year survival rates of patients with the different types of ATL are shown in Fig. 4.3. The survival curve of patients with pleomorphic (medium- and large-cell)-type lesions, which display features typical of ATL, rapidly decreases, during both the early and late stages of the disease (Fig. 4.4). ATL manifested by anaplastic large-cell- and AILT-type lesions is also associated with a highly aggressive course; most patients die within 2 years after diagnosis. ATL with Hodgkin-type lesions was found to be associated with a progressively decreasing survival curve during an observation period of 8 years. Pleomorphic small-cell-type lymphoma has been associated with an initial steep increase in mortality, with plateauing of the rate during the middle and later observation periods. On the other hand, all cases with lymphadenitis were alive at the end of one study (Fig. 4.3) [13].

4.1.4 Cutaneous Lesions

ATL commonly involves the skin, as well as the peripheral circulatory system and lymph nodes. Cutaneous lesions related to ATL are polymorphous in appearance. Skin lesions are frequently observed in all the clinical subtypes. The prevalence of lesions reportedly ranges from 43% to 72% [21]. Furthermore, some reports have described patients who presented with cutaneous lesions only, remaining free for many years of leukemic changes or visceral invasion [22, 23]. Johno et al. [22] proposed a new category of ATL, cutaneous ATL (cATL), manifested throughout the entire course of disease by persistent skin lesions and which does not easily progress to leukemia or nodal lymphoma. Their findings also indicate that the prognosis of the tumoral type of ATL (MST: 26 months) is worse than that of the erythematopapular type (80 months) [22].

We previously investigated the HTLV-I proviral status and clinicopathological features of the cutaneous lesions of 80 cases with serum anti-ATL antibody (ATLA) to evaluate the relationship between the macroscopic/histopathological findings of the patients and patient outcome [23]. The MST of patients with the provirus was found to be 14 months, which was markedly shorter than the MST of patients negative for integrated proviral DNA (72 months). Of 46 cases with

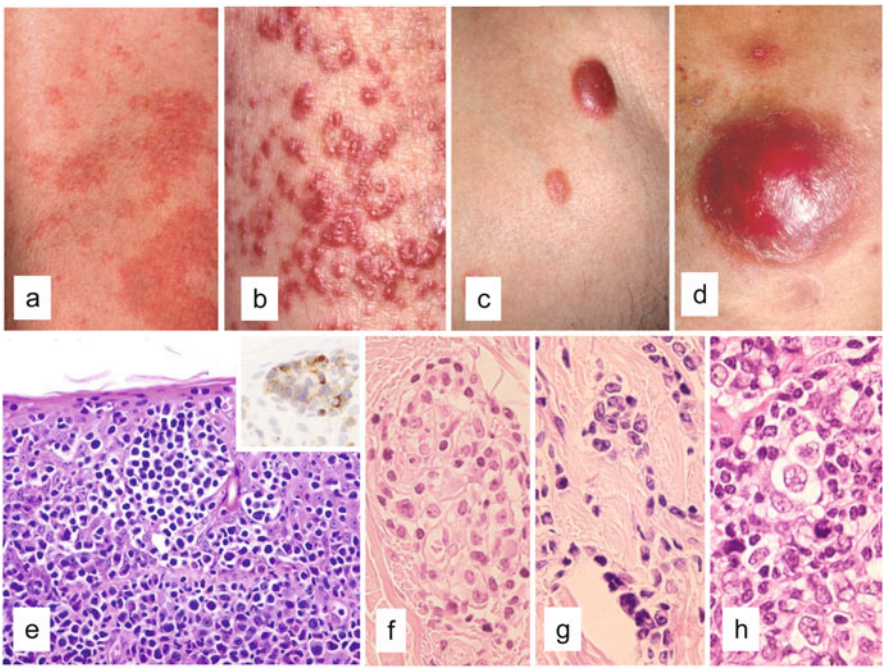

Fig. 4.5 Macroscopic/histopathological findings of skin. (**a**) The macroscopic findings have been classified as erythema (**a**), papules (**b**), nodules (**c**), and tumor (**d**). Histopathological findings. The lymphoma cells have infiltrated the epidermis, producing Pautrier-like microabscesses. The lymphoma cells react with CD3 antibody (*inset*) (**e**). The lymphoma cell sizes are varied to small (**f**), medium sized (**g**), and large (**h**)

proviral DNA, 21 had solitary or multiple red nodules (including 3 with subcutaneous induration), 8 had multiple red papules, and 17 had erythema (Fig. 4.5). Patients with papules and tumors tended to have worse outcomes than those with erythema (Fig. 4.6).

Histopathological examination of the biopsy tissue from the erythematous lesions of the cases found perivascular or diffuse infiltration in the upper dermis by small- to medium-sized atypical lymphoid cells with mild to moderate nuclear atypia (Fig. 4.5). Mitotic figures were few in number. These atypical lymphoid cells had the phenotypes of peripheral T cells (CD1-, CD2+, CD3+, 45RO+, and usually CD4+) [21–23].

Histopathological examination of the biopsy tissue from nodular lesions of cases with nodules found infiltration by medium- to large-sized atypical lymphoid cells with round or irregular nuclei and small nucleoli. Mitotic figures were occasionally encountered. Biopsy tissue with a diffuse infiltration pattern also manifested atypical medium- to large-sized lymphoid cells. The outcome of patients with nodular or diffuse infiltration by medium- to large-sized lymphoma cells was worse than the

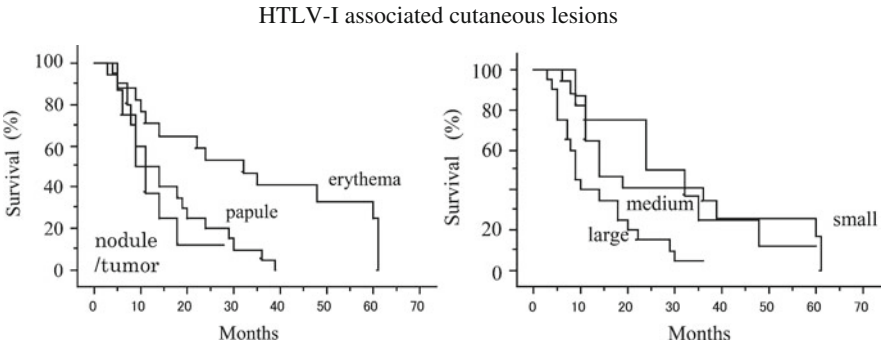

Fig. 4.6 Survival of cutaneous lesions. Patients with papules, nodules, and tumors have poorer prognosis than those with erythema. The large-cell type have poorer prognosis than small and medium-sized type (Adapted from Ref. [23])

outcome of those with perivascular infiltration by small- to medium-sized lymphoma cells (Figs. 4.5 and 4.6) [23].

The macroscopic findings were fairly similar to the histopathological findings. The nodular lesions of cases with nodules showed nodular infiltration. The papular lesions showed nodular or diffuse infiltration. The erythematous lesions showed diffuse or perivascular infiltration. In this series of 80 cases, patients with nodules and papules had a worse outcome than those with erythema, and the histopathological analysis found that patients with nodular infiltration by atypical lymphoid cells had the worst outcome (MST: 9 months). The outcome of patients with diffusely infiltrated lesions (MST: 20 months) was somewhat better than the outcome of patients with perivascular infiltration of their lesions (MST: 24 months) [23].

4.1.5 Gastrointestinal Tract

The results of a few studies have suggested that HTLV-I may also be involved in the development of gastrointestinal T-cell lymphoma (GTL) [24, 25]. Sakata et al. [25] reported that 23–78% of ATL cases showed stomach invasion, and almost all of these patients were in an advanced clinical stage of the disease. While these findings indicate that gastric invasion by ATL cells occurs frequently during the advanced stage of ATL, there have also been reports of a few early-stage ATL cases with HTLV-I-associated GTL.

We analyzed 15 patients with HTLV-I-associated GTL [26]. The gastric lesions were located in the upper or middle corpus in eight cases and widely distributed in seven. Macroscopic examinations found ulcerated masses, erosions, or tumors. Histopathological examination found three types of lesions. One type showed diffuse infiltration by atypical medium-sized lymphoid cells with round or irregular

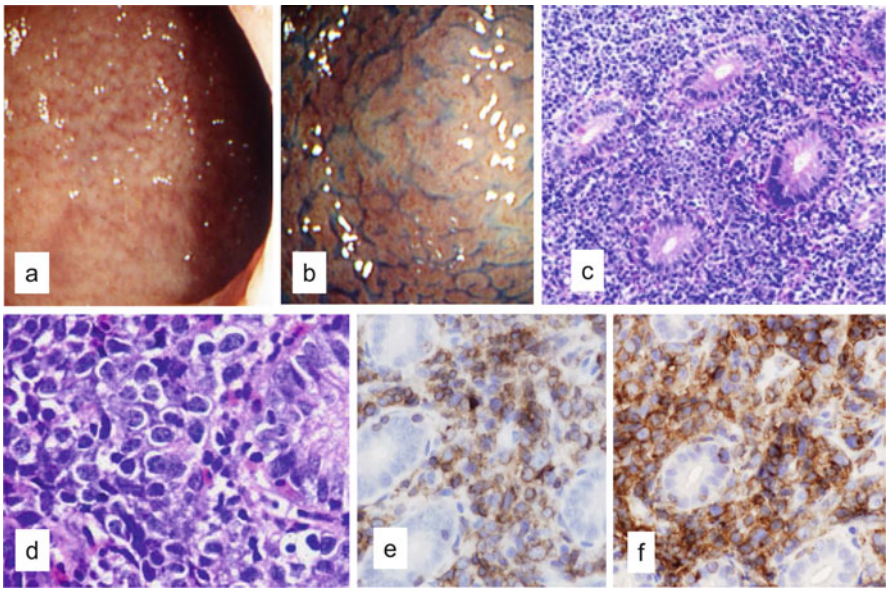

Fig. 4.7 Macroscopic/histopathological findings of gastrointestinal tracts. (**a**) Endoscopy demonstrated edematous and reddish mucosa in large intestine. (**b**) The spreading methylene blue on the mucosa surface enabled to discriminate the lesions. (**c**) The large intestine shows a diffuse infiltration of lymphoma cells in the mucosa. (**d**) The lymphoma cells are pleomorphic medium-sized and large-cell type. The lymphoma cells react with CD3 (**e**) and CD4 (**f**) antibody

nuclei. A second type showed diffuse infiltration by medium- and large-sized pleomorphic lymphoid cells with round or irregular nuclei. The third type, which occurred in rare cases, had diffuse proliferation of large to giant anaplastic cells with round or lobulated nuclei, distinct nucleoli, and abundant cytoplasm. Cohesive growth patterns were detected (Figs. 4.7 and 4.8). Among all three types, the destruction of gastric glands by infiltrating lymphoma cells was obvious. These patients all had poor outcomes, dying within 2 years of treatment. Four cases in this series showed no evidence of leukemic changes, but nine cases showed atypical lymphoid cells in the peripheral blood (1–2% of lymphocytes were atypical) [26]. Rare cases showed small and large intestinal lesions, which appeared on endoscopy as multiple ulcers or erosive changes [24].

4.1.6 Liver

ATL involvement of the liver is mainly seen in the portal area, which shows infiltration by atypical medium- to large-sized lymphoid cells with irregular nuclei. Destruction of the limiting plate of hepatocytes is occasionally seen, and in some

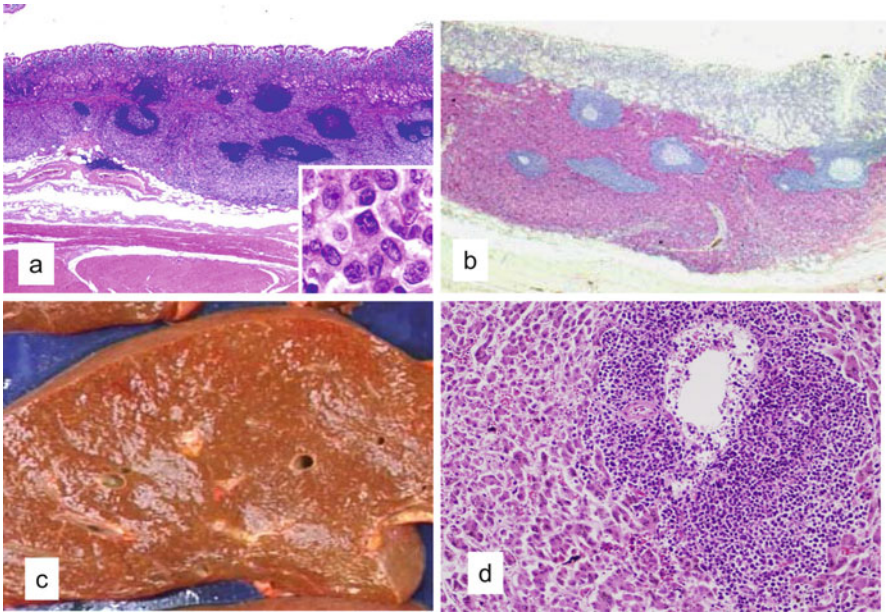

Fig. 4.8 Histological findings of stomach and liver. (**a**) The stomach shows a tumorous lesion with a diffuse proliferation of lymphoma cells with anaplastic large-cell features (inset). (**b**) The lymphoma cells react with CD3. (**c**) The liver shows diffuse swelling but no local lesions. (**d**) The portal area of the liver shows a diffuse infiltration of atypical lymphoid cells

cases, there is sinus infiltration. Fibrosis is rare (Fig. 4.8c, d). Mitotic features are occasionally encountered. [14]

4.1.7 Bone Marrow

ATL involvement of the bone marrow is occasionally seen, even in cases with a leukemic blood picture, as are patchy infiltrates of atypical lymphoid cells with irregular or round nuclei in the marrow cavity, sometimes near bone trabeculae. Clinically, hypercalcemia is an important laboratory finding associated with ATL. Absorption of bone accompanied by periosteal fibrosis, such as seen in osteitis fibrosa generalisata, may or may not be accompanied by tumor cell infiltrates (Fig. 4.9). Increased numbers of osteoclasts are sometimes seen in the peritrabecular spaces (Fig. 4.9) [14].

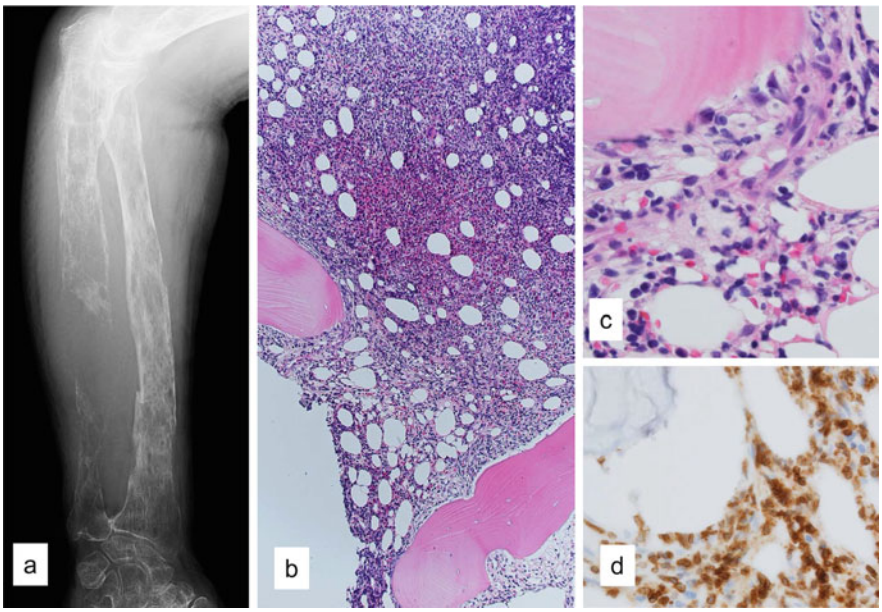

Fig. 4.9 Bone and bone marrow of ATL. (**a**) A radiograph of the leg shows extensive lytic bone lesions. (**b**) The bone marrow shows diffuse infiltration of lymphoma cells. (**c**) The lymphoma cells are pleomorphic medium-sized and large-cell type. And osteoclasts of the peri-trabeculae are increased in number. (**d**) The lymphoma cells react with CD3 antibody

4.2 Nonneoplastic Lesions

4.2.1 HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP)

The first symptoms are weakness of the lower limbs and lumbar pain, although the initial complaint can be sensory in nature, such as tingling, burning, or pins and needles. Urinary and sexual problems can also be initial symptoms [27].

The disease mainly affects the spinal cord, particularly the lateral and anterior columns, where bilateral loss of myelin and axons has been observed, mainly along the neural tract. Perivascular and parenchymal infiltration by lymphocytes and macrophages, as well as astrocytosis, have been found in the white and gray matter of the spinal cord, while blood vessels in the spinal cord and in the subarachnoid space of the spinal cord have shown hyaline thickening of the media and adventitia, associated with infiltrating lymphocytes (Fig. 4.10a). The lymphocytes have not shown nuclear atypia, and mitotic figures have rarely been encountered. The spinal lesion is associated with dense perivascular mononuclear cell infiltrates, largely CD8+ lymphocytes [28].

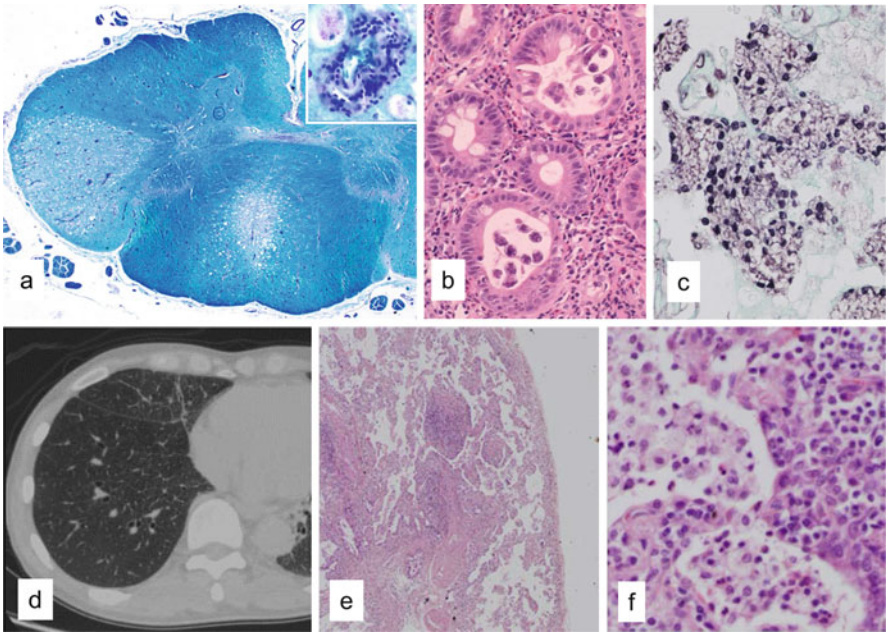

Fig. 4.10 Histology of HAM and immunodeficient disorders. (**a**) HAM mainly affects the spinal cord, particularly the lateral and anterior columns, where loss of myelin and axon, accompanied by dense lymphocytic perivascular infiltration (inset) (Kluver-Barrera staining). (**b**) Strongyloides stercoralis was detected in the gastric glands. (**c**) Pneumocystis carinii was identified in the alveolar spaces by means of Grocott staining. (**d**) HTLV-I-associated bronchopneumopathy (HAB) displays diffuse reticular shadow in CT. (**e**) The histology shows a proliferation of bronchial mucosa epithelium with an infiltration of lymphocytes. (**f**) The lymphocytes show no nuclear atypia

4.2.2 HTLV-I-Associated Uveitis (HAU)

Based on seroepidemiological, clinical, and virological data, it can be concluded that HTLV-I is closely associated with a certain type of uveitis. Uveitis is a vision-threatening inflammatory disorder affecting the intraocular tissues (iris, ciliary body, vitreous body, optic nerve, retina, choroid). Histopathological examination has found that the intraocular tissues are infiltrated by a number of inflammatory cells, including lymphocytes and histiocytes. The lesion is characterized by a granulomatous or nongranulomatous reaction accompanied by vitreous opacity and retinal vasculitis. The lymphocytes do not show nuclear atypia, and mitotic figures are rarely encountered. [29]

4.2.3 HTLV-I-Associated Bronchopneumopathy or Diffuse Panbronchiolitis (HAB)

Kimura et al. [30] reported that some individuals with idiopathic interstitial pneumonia and diffuse panbronchiolitis possessed an anti-ATL antibody (ATLA). They postulated an association between HTLV-I infection and idiopathic interstitial pneumonia and diffuse panbronchiolitis.

Histopathologically, there is a proliferation of bronchial epithelial mucosa accompanied by thickening of the basement membrane and an infiltrate in the epithelial layer and mucosa propria, predominantly consisting of lymphocytes together with some plasma cells, histiocytes, and neutrophils (Fig. 4.10d–f). The lymphocytes are usually small; and nuclear atypia and mitotic features are rare, while in the alveolar areas there is mild fibrosis and edema of the alveolar wall and infiltration by lymphocytes and some plasma cells.

In cases with leukemia/lymphoma invasion, however, there is prominent diffuse infiltration by atypical lymphocytes with irregular nuclei. Nodular proliferation is also present in these cases.

4.2.4 Opportunistic Infections

Opportunistic infections occur frequently in patients with ATL [4]. In addition, HTLV-I-infected carriers seem to have an increased risk of strongyloidiasis, which suggests a possible subclinical immunodeficiency. HTLV-I-infected individuals from areas where *Strongyloides stercoralis* is highly endemic should probably have regular fecal examinations (Fig. 4.10b, c). Other reported infections associated with HTLV-I carriers include crusted scabies, disseminated molluscum contagiosum, and extrapulmonary histoplasmosis [4].

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