findings of MF are difficult to obtain at the early stages, skin biopsies may be conducted repeatedly at certain intervals in suspected cases. Immunohistological tests are conducted on the biopsy specimen: The surface marker of helper T-cells is confirmed in the infiltrating lymphocytes. Monoclonality of T-cell receptor gene rearrangement is identified (MEMO). Dermatitis, psoriasis, parapsoriasis, adult T-cell leukemia, and other types of malignant lymphoma are differentiated from MF.

Phototherapies such as PUVA and narrow-band UVB inhibit the progression of lesions in the patch and plaque stages to some extent. Topical steroids and interferon are also useful. For progressive cases such as MF in the tumor stage, electron beam irradiation and chemotherapy (e.g., CHOP therapy; the treatment is the same as for non-Hodgkin’s disease; Table 22.7) are performed.

### Gene rearrangement analysis

Rearrangement of the TCR and immunoglobulin (Ig) genes occurs during lymphocyte differentiation for recognition of non-self, which leads to various antigenic recognitions. In lymphoma, lymphocytes proliferate monoclonally and there is often one rearrangement pattern to the TCR/Ig gene. Thus, southern blotting from skin lesion tissue is useful for differentiating between lymphoma and benign diseases. When the gene encoding TCR/Ig is excised by a restriction enzyme and the tissue is lymphoma (monoclonal), a single band is observed in electrophoresis; in the case of a benign reactive disease (polyclonal), there is no specific band in electrophoresis. These findings are helpful for diagnosing the malignancy of tissues and blood (gene rearrangement analysis, GRA).

GRA of the J\(\gamma\) chain and the C\(\beta\)1 chain of the TCR gene are performed in T-cell lymphoma. A similar analysis is made for diagnosis of B-cell lymphoma, using southern blotting for Ig\(H\)-J\(\mu\), a gene that codes for an immunoglobulin fragment.

### Treatment

Phototherapies such as PUVA and narrow-band UVB inhibit the progression of lesions in the patch and plaque stages to some extent. Topical steroids and interferon are also useful. For progressive cases such as MF in the tumor stage, electron beam irradiation and chemotherapy (e.g., CHOP therapy; the treatment is the same as for non-Hodgkin’s disease; Table 22.7) are performed.

### 2. Sézary syndrome (SS)

### Outline

- It is a T-cell lymphoma that occurs primarily in skin, lymph nodes and peripheral blood.

---

**Fig. 22.36-2 Mycosis fungoides.**

d, e: Plaque stage. f-j: Tumor stage. Severely infiltrative ulcers form.
Intense itching is present. The main symptoms are erythroderma, swelling of lymph nodes and the appearance of atypical lymphocytes in the peripheral blood.

**Clinical features**

Men over age 50 are most frequently affected by Sézary syndrome (SS). Erythema accompanied by scaling on the whole body surface occurs diffusely, presenting as erythroderma (Fig. 22.38). Intense itching is often present. There is enlargement of lymph nodes and splenohepatomegaly. The systemic symptoms tend to be mild, and fever is not present. As SS progresses, nodular eruptions occur and may infiltrate into the internal organs.

**Pathology, Laboratory findings**

Leukocytosis and lymphocyte atypicality are found in the peripheral blood. These atypical lymphocytes, called Sézary cells, have a nucleus with a deep slit as seen in the cells found in tissue with mycosis fungoides, and they contain superficial markers of helper T cells. Band-like or perivascular lymphocytic infiltration including Sézary cells are found in the upper dermal layer of the areas with erythroderma. Pautrier’s microabscess may occur in the epidermis (Fig. 22.36).

**Treatment**

The treatments are the same as for mycosis fungoides. The prognosis is generally worse than that of mycosis fungoides.

### 3. Primary cutaneous anaplastic large-cell lymphoma

This is a T-cell lymphoma caused by infiltration of CD30-positive lymphocytes. Solitary nodules or papules, tumors that may ulcerate, and infiltrative erythema occur (Fig. 22.39). Pathologically, there is infiltration of atypical cells and histological morphology of undifferentiated large tumor cells resembling that of Hodgkin’s disease. Diagnosis of primary cutaneous anaplastic large-cell lymphoma (ALCL) is confirmed if the tumor cells react to anti-CD30 antibodies (Ki-1 antibodies). When cutaneous lymphomas including mycosis fungoides, Sézary syndrome or
adult T-cell leukemia/lymphoma are present as a precursor or a current symptom, the condition is not diagnosed as ALCL even if there is infiltration of CD30-positive cells in the skin lesion. The prognosis is generally good.

**Supplement: Lymphomatoid papulosis**

Lymphomatoid papulosis begins as papules of several millimeters to 1 cm in diameter, usually several to several dozen in number, which are accompanied by scaling and bloody crusts. The center of the papules may be necrotic or crusted. The papules may reach several centimeters in diameter. The eruptions heal spontaneously in 2 to 3 weeks, with moderate scarring and pigmentation (Fig. 22.40). Infiltrative atypical cells are CD30-positive. Histopathologically, there is infiltration of polymorphic lymphocytes whose atypical chromatin stains deeply, cellular division, leakage of erythrocytes, and eosinophilic infiltration: These findings seem to suggest malignancy. However, whether lymphomatoid papulosis is a benign disease or a subtype of ALCL is still controversial. Mycosis fungoides or other lymphoma occurs as a complication in fewer than 20% of cases. When it does not heal spontaneously, topical steroids and PUVA therapy are applied.

### 4. Pagetoid reticulosis (Woringer-Kolopp) *

Tumor cells are markedly epidermotropic and resemble Paget’s cells. Clinically distinctive parapsoriasis-like or psoriasis-like plaques form. Pagetoid reticulosis is considered to be a specific type of mycosis fungoides.

### 5. Adult T-cell leukemia/lymphoma (ATLL) *

**Outline**

- It is a hematopoietic malignancy caused by human T-cell leukemia virus type-1 (HTLV-1).
- Multiple, firm, reddish-brown skin tumors with dome-shaped elevation appear. Erythroderma and elevated, scaling plaques form.
- Serum anti-HTLV-1 antibodies are positive. Characteristic “flower cells” are found in the peripheral blood.

**Clinical features**

Adult T-cell leukemia/lymphoma (ATLL) is classified by the course into several types, including smoldering, chronic, acute and lymphoma types. Cutaneous lesions may be seen in all variants. Multiple, firm, dome-shaped, reddish-brown tumors ranging in size from several millimeters to 10 cm occur. They may be accompanied by scaling, infiltrative elevated reddish-brown plaques, and erythroderma (Figs. 22.41-1 and 22.41-2). Besides
the characteristic eruptions, non-specific eruptions caused by immunodeficiency, various infections such as mycosis and herpes zoster, erythema, urticaria, acquired ichthyosis, palmoplantar keratosis and eczema-like eruptions also appear. There are systemic symptoms such as fever, lymph node enlargement, and splenomegaly. As ATLL progresses, opportunistic infection is caused by fungus or virus resulting from cellular immunodeficiency.

The main complications are HTLV-1-associated myelopathy (HAM/TSP), HTLV-1-associated arthropathy (HAAP), and HTLV-1-associated uveitis.

**Epidemiology**

The incidence varies by region. In Japan, about 1.2 million persons have tested positive for anti-HTLV-1 antibodies, and it is estimated that 500 to 600 of these persons will develop ATLL every year. Worldwide, many patients are from the Caribbean and parts of Africa.

The routes of infection may be through sexual activity or blood. Most cases are transmitted materno-fetal by breast milk. In sexual activity, it is transmitted from male to female in semen. The incubation period between transmission and development of ATLL is usually more than 40 years. Most persons who are infected in infancy do not have the symptoms throughout life. Most patients are over age forty. Cases in youths are rare.

**Pathogenesis**

HTLV-1, an RNA virus, is known to induce monoclonal proliferation of T cells. HTLV-1 proviral DNA is integrated in the malignant T cells.

**Laboratory findings, Diagnosis**

Serum anti-HTLV-1 antibodies are positive. The antibody titer is measured first for diagnosis. For patients whose serum is positive for anti-HTLV-1 antibodies, Southern blot is performed to identify monoclonal integration of HTLV-1 proviral DNA into tumor cells. There is a marked increase of leukocytes and atypical lymphocytes called flower cells in the peripheral blood (Fig. 22.42), increased LDH in the blood from tumor cell destruction, increased serum Ca, and increased soluble IL-2 receptor. ATLL is classified into subtypes according to the severity of these changes (Table 22.8).

**Treatment, Prognosis**

Follow-ups are given to patients with chronic and smoldering types of ATLL, to check for any signs of acute transformation. The acute, lymphoma, and acute transformation types are treated with conventional chemotherapy. The prognosis is remarkably poor, most patients dying within 2 years from the initiation of treatment. Pneumocystis carinii pneumonia is treated by preventive administration of trimethoprim-sulfamethoxazole combination.
IV fluid and calcitonin are administered for hypercalcemia.

### 6. Natural killer (NK)/T-cell lymphoma

In natural killer (NK)/T-cell lymphoma, abnormally increased NK/T-cells damage various normal tissue cells, resulting in the clinical appearance of destruction, such as ulcers. NK cells may be difficult to distinguish from T cells and are sometimes described as NK/T cells. A hydroa vacciniforme-like eruption that is associated with viral infection, chronic active Epstein-Barr (EB) virus infection and hypersensitivity to mosquito bites may progress to NK/T-cell lymphoma several years to several decades after onset.

**Extranodal nasal T/NK-cell lymphoma (lethal midline granuloma):** This is a typical type of extranodal T/NK cell lymphoma. It occurs in the nasopharynx region. The positivity of an NK cell marker (CD56) in the lymphoma cells is typical. There is an association between EB virus and extranodal nasal T/NK-cell lymphoma. It may be misdiagnosed as sinusitis resulting from rhinophonia. Cutaneous symptoms are panniculitis-like lesions that are prone to ulceration (Fig. 22.43), swelling in the eyelids, face and lips, aphtha in the lips, and chilblain-like eruptions. Cases with multiple lesions or infiltration in multiple organs have

| Table 22.8 Clinical characteristics and types of adult T-cell leukemia/lymphoma. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Smoldering      | Chronic         | Lymphoma        | Acute           |
| Anti-HTLV-1 antibody           | +               | +               | +               | +               |
| Number of lymphocytes (x10⁹/L) | <4              | ≥4a             | <4              | *               |
| Atypical T-cells               | ≥5%             | +               | ≤1%             | +               |
| Flower cells                   | Often           | Often           | None            | +               |
| LDH                            | ≤1.5N           | ≤2N             | *               | *               |
| Ca concentration (mg/dl)       | <11             | <11             | *               | *               |
| Lymph node infiltration        | None            | *               | +               | *               |
| **Tumor**                      | **Skin**        | ****            | **Lungs**       | ****            |
| **Liver**                      | None            | *               | *               | *               |
| **Spleen**                     | None            | *               | *               | *               |
| **Central nervous system**     | None            | None            | *               | *               |
| **Bones**                      | None            | None            | *               | *               |
| **Ascites**                    | None            | None            | *               | *               |
| **Pleural effusion**           | None            | None            | *               | *               |
| **Digestive tract**            | None            | None            | *               | *               |

N: Uppermost normal value, *: Unnecessary for diagnosis, **: Necessary for diagnosis of cases in which peripheral atypical T cells account for 5% or less of total leukocytes. a: T lymphocyte density is 3.5x10⁹/L or more.
b: When atypical T lymphocytes account for 5% or less of total leukocytes, histological diagnosis is necessary.
a poor prognosis.  

**CD4+/CD56+ hematodermic neoplasm (blastic NK cell lymphoma):** This is caused by NK precursor cells. It is not associated with the EB virus. The pathogenesis is unknown. A purplish red, infiltrative erythematous plaque or tumor occurs.  

**Lymphoma associated with hydroa vacciniforme:** Hydroa vacciniforme used to be attributed to photosensitivity (Chapter 13); the cause is now thought to be proliferation of NK/T cells from EB viral infection. Papules or blisters accompanied by central umbilication and necrosis occur on sun-exposed areas such as the dorsal hands and cheeks. Edema appears on the eyelids, lips and face.

### 7. Subcutaneous panniculitis-like T-cell lymphoma

Panniculitis-like clinical features resemble those of erythema nodosum (Fig. 22.44). The tumor cells derive from cytotoxic T cells. The prognosis is poor. It may worsen rapidly in some cases.

### Cutaneous B-cell lymphoma

Cutaneous B-cell lymphoma that remains localized in the skin at the time of diagnosis is called primary cutaneous B-cell lymphoma (PCBCL). The classification of cutaneous B-cell lymphoma has not been completely clarified; however, terminology adopted from the WHO/EORTC classification is widely used (Table 22.6). The main subtypes of PCBCL are follicle center lymphoma, marginal-zone B-cell lymphoma, and diffuse large B-cell lymphoma.

A nodule or tumor appears solitarily, leading to a localized red or purplish-red plaque. Multiple papules, nodules or infiltrating erythema occur in some cases. The eruption rarely ulcerates. Although the skin surface is normal, erosive lymphocytic infiltration occurs in the dermis; the deeper the infiltration, the severer it tends to be (bottom-heavy appearance). B-cell-specific antigens are expressed, and T-cell surface antigens are not detected (Table 22.9). When single B-cells abnormally proliferate, monoclonality of immunoglobulin gene becomes apparent; gene rearrangement analysis (described previously; MEMO) is useful for differential diagnosis. The main treatment is radiation therapy. Chemotherapy and CD20 monoclonal antibodies (rituximab) are administered in cases with multiple lesions.

### 1. Primary cutaneous marginal zone B-cell lymphoma

The trunk and extremities are most frequently affected. The tumor is composed of the cells that form the marginal zone, mature B cells that passed the germinal center, and plasma cells (Fig. 22.45). 5-year survival rate is almost 100%. The main treatments are excision and radiation.
2. Primary cutaneous follicle center lymphoma

The head, neck, and trunk are most frequently involved. There is proliferation of the centrocytes or centroblast-like cells that are normally seen in lymphoid follicles. The prognosis is good; the 5-year survival rate is 95%. The main treatments are excision and radiation (Fig. 22.46).

3. Primary cutaneous diffuse large B-cell lymphoma

It occurs most commonly on the lower legs of elderly people. There is proliferation of centroblasts and/or immunoblasts. The prognosis is rather poor; the 5-year survival rate is 50% to 70%. The first line treatment is chemotherapy (Fig. 22.47).

e-2. Leukemia cutis

This specific eruption is caused by infiltration of leukemic tumor cells from blood into the skin. Papules, nodules, tumors and erythroderma are the main cutaneous symptoms (Fig. 22.48). It occurs frequently in adult T-cell leukemia, acute monocytic leukemia, and acute transformation of chronic myelogenous leukemia. Skin lesions that accompany leukemia but are not caused by direct infiltration of tumor cells are called non-specific.

Table 22.9 Differentiation of B cells and cellular surface traits.

<table>
<thead>
<tr>
<th>Mature phase</th>
<th>Tumor</th>
<th>TdT</th>
<th>Cellular surface trait</th>
<th>clg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic stem cell</td>
<td>B-ALL</td>
<td>+</td>
<td>CD19, CD10, CD20</td>
<td>H^bL_R^O</td>
</tr>
<tr>
<td></td>
<td>B-ALL, CLL</td>
<td>+</td>
<td>CD19, CD20, CD21, IgM</td>
<td>H^bL_R^O</td>
</tr>
<tr>
<td>Pro B cell</td>
<td>B-ALL, CLL</td>
<td>+</td>
<td>CD19, CD10, CD20, IgM</td>
<td>H^bL_R^O</td>
</tr>
<tr>
<td>Pre B cell</td>
<td>B-ALL, CLL</td>
<td>+</td>
<td>CD19, CD20, CD21, IgM</td>
<td>H^bL_R^O</td>
</tr>
<tr>
<td>Immature B cell</td>
<td>CLL</td>
<td></td>
<td>CD19, CD20, CD21, IgM, IgD, Fc, (CD5)</td>
<td>I^g</td>
</tr>
<tr>
<td>Mature B cell</td>
<td>ML, PL, HCL</td>
<td></td>
<td>CD19, CD20, (CD21), Fc, (CD10), CD35, IgG, IgA, IgM</td>
<td>I^g</td>
</tr>
<tr>
<td>Plasma-cell-like B cell</td>
<td>ML, MG, HCL</td>
<td></td>
<td>CD19, CD20, CD35, CD38, IgM, Fc, PCA-1, (PC-1)</td>
<td>I^g</td>
</tr>
<tr>
<td>Plasma cell</td>
<td>MM</td>
<td></td>
<td>CD38, PC-1, PCA-1</td>
<td>I^g</td>
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</tbody>
</table>
