Tumors, whether malignant or benign, should be examined to determine the skin component from which they originate. The clinical features, course of progression, and prognosis differ according to the cells from which the tumor derives. Malignant skin tumors may derive from 1 epidermal or follicular keratinocytes, 2 intradermal mesenchymal cells, 3 skin appendages such as sweat glands, or 4 neural crest cells. Benign tumors described in Chapter 21 may become malignant and have malignant diagnostic names. This chapter introduces malignant tumors that have relatively high incidences.

### Malignant skin tumors

#### A. Epidermal and follicular tumors

1. **Basal cell carcinoma (BCC)**

   **Synonym:** Basal cell epithelioma

   **Outline**

   - It is a malignant skin tumor whose incidence is high.
   - It is induced by UV and occurs most commonly in the elderly, on the midline of the face.
   - Small grayish-black nodules arrange themselves at the edge of the tumor. The center of the tumor may be ulcerative.
   - Localized intense infiltration may be present. Metastasis rarely occurs. The prognosis is good.
   - Excision is the basic treatment.

   **Clinical features**

   Basal cell carcinoma (BCC) occurs most frequently in men and women aged 40 to 60. In all subtypes, there are small, firm, waxy, glossy, blackish-brown nodules at the periphery of the skin lesion (Fig. 22.1). Telangiectasia often occurs in the lesion and at the periphery. The face, especially its midline, is affected in 80% of cases; the most notable exceptions to this are the superficial type and fibroepithelial basal cell carcinoma of Pinkus, which often appear on the trunk. The lesion appears blackish-brown in most cases in Asians; however, it is usually normal skin color in Caucasians. BCC may manifest various subtypes and clinical features.

   **Ulceronodular type:** More than 80% of BCCs are of this type. Small, firm, black nodules coalesce, accompanied by epidermal telangiectasia. The center of the lesion often ulcerates (rodent ulcer).

   **Superficial type:** A flatly elevated, infiltrative plaque ranging in
color from red to blackish brown gradually expands.

**Sclerosing type (morphea-form):** It is an oval, infiltrative plaque with a slightly concave center.

**Pinkus type (fibroepithelial basal cell carcinoma of Pinkus):** Small, multiple, pedunculated tumors occur, often in the midline of the lumbar and back sacral region. This type is histopathologically diagnosed; it is characterized by deeply expanded strands of tumor cells within fibrous stromata.

**Pathogenesis**

BCC results from proliferation of embryonic epithelium (primary epithelial germ cells) that differentiates into various organs. There are hamartomatous factors; however, embryonic epithelium continues to proliferate, destroying normal tissue.

---

**Fig. 22.1 Various clinical types of basal cell carcinoma (BCC).**

a-j: Nodular BCC. k, l: Superficial BCC. m: BCC. Because the BCC was left untreated, it damaged the bone and infiltrated into the brain. n: BCC infiltrated into the eyeball. o: Morphea-form BCC.

**Fig. 22.2-1 Basal cell carcinoma (BCC) from underlying disease.**
a: BCC in a patient with xeroderma pigmentosum (group D).
Sunlight, traumatic injury, radiation and scarring are associated with the occurrence of BCC. It may occur secondarily with an underlying disease, such as xeroderma pigmentosum, basal cell nevus syndrome, chronic radiodermatitis, chronic arsenic poisoning, or nevus sebaceous. In such cases, the young may also be affected, and the skin lesions are multiple (Figs. 22.2-1 and 22.2-2).

**Pathology**

BCC is the proliferation of tumor cells that resemble epidermal basal cells (Fig. 22.3). The cells have a large oval nucleus, a small amount of cytoplasm, and low atypicality. The tumor cells arrange in a palisading pattern (palisading arrangement) at the periphery. Connective tissue and mucin proliferate around the tumor. BCC is characterized by the presence of spaces between tumor and stroma that result from sectioning (separation artifact). Epidermis-derived and follicle-derived melanocytes are found mingled. The abundance of melanophages in the stroma results in the clinical blackish color. BCCs are histopathologically divided into nodular, adenoid, keratotic, cystic and other types (Fig. 22.4).

**Differential diagnosis**

BCC should be differentiated from lentigo, blue nevus, Spitz nevus, seborrheic keratosis, chronic ulcer and chronic granuloma. Dermoscopy is useful in many cases (Chapter 5). The superficial type is further differentiated from psoriasis and Bowen’s disease. The sclerosing type is differentiated from localized scleroderma, discoid lupus erythematosus, granuloma annulare and keloid.

**Treatment**

Surgical removal is the basic treatment. As the face is frequently affected, cosmetic surgery may be necessary. Cryotherapy and topical chemotherapy may be chosen.

**Prognosis**

BCC does not metastasize in general: The prognosis is good. However, it continues proliferating, destroying normal tissue unless excised. Surgical treatment at an early stage is preferable.
2. Squamous cell carcinoma (SCC)

Synonym: Squamous cell cancer

**Outline**

- This cancer is caused by malignant proliferation of epidermal keratinocytes.
- In situ lesions including those of solar keratosis and Bowen’s disease are often caused. Scarring lesions are sometimes accompanied by SCC.
- There is often a preexisting lesion, such as scarring or precancerous lesion.
- A firm nodule occurs, frequently on a sun-exposed area of the body. It often necrotizes and ulcerates, and gives off a foul odor.
- Pathologically, individual cell keratinization and cancer pearls are seen. The less keratinous are the cells, the more undifferentiated and malignant the cancer is.
- Surgical removal, lymph node dissection, radiation therapy and chemotherapy are the main treatments.

**Clinical features**

Squamous cell carcinoma (SCC) occurs in the elderly solitarily on sun-exposed areas of the body, such as the face and dorsum of hands. Small papules and nodules appear on preexisting lesions, gradually extend, and form tumors or intractable ulcers (Figs. 22.5-1 and 22.5-2). They proliferate, taking on a cabbage-like appearance. The skin lesion is often accompanied by keratinous substance and crusts. When the surface of the lesion ulcerates, bacterial secondary infection accompanied by distinct odor occurs. SCC tends to spread to the regional lymph node, which then feels firm when palpated.

**Pathogenesis**

SCC frequently occurs on a preexisting chronic epidermal lesion. In addition to the preceding lesions shown in Table 22.1, carcinogenic factors such as exposure to sun (UV), arsenic, tar and irradiation are associated with the onset.

<table>
<thead>
<tr>
<th>Table 22.1 Preexisting lesions of squamous cell carcinoma (SCC).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of disease</strong></td>
</tr>
<tr>
<td>Scarring</td>
</tr>
<tr>
<td>Precancerous</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Fig. 22.5-1 Squamous cell carcinoma (SCC).

a: Actinic keratosis progressed to SCC. b: SCC on the lower lip. c: SCC on the abdominal region. d: SCC on the buttocks. e: SCC on the dorsum of the hand.
Abnormal keratinocytes that destroy the epidermal basal layer are found within the infiltrative and thickened epidermis (Fig. 22.6). SCC is characterized by individual cell keratinization, disturbance in cellular arrangement, nuclear atypicality, cancer pearls and cellular division. The more undifferentiated and malignant are the cells, the less keratinization may occur.

**Differential diagnosis**

Lymph node involvement and distant metastasis are examined by image analysis to identify the disease stage (TNM classification, Table 22.2). Keratoacanthoma, actinic keratosis and basal cell carcinoma are differentiated from SCC.

**Treatment**

Surgical removal is the first-line treatment. Lesions are excised together with 4 mm to 10 mm of adjoining normal skin. Radical lymph node dissection is conducted in cases with lymph node involvement. However, prophylactic lymph node dissection tends not to be conducted. Combined modality therapies, such as irradiation therapy and chemotherapy (Fig. 22.7), are conducted on progressive cases.

### Table 22.2 TNM classification and stage grouping of SCC (UICC, 2002).

<table>
<thead>
<tr>
<th>T classification (primary lesion)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Primary lesion is not found.</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Lesions of 2 cm or less in diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Lesions of 2 cm to 5 cm in diameter</td>
</tr>
<tr>
<td>T3</td>
<td>Lesions of 5 cm or more in diameter</td>
</tr>
<tr>
<td>T4</td>
<td>Lesions that invade tissues deeper than skin (e.g., cartilage, muscle, bone)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N classification (regional lymph nodes)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Lesions without metastasis in regional lymph node</td>
</tr>
<tr>
<td>N1</td>
<td>Lesions with metastasis in regional lymph node</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M classification (distant metastasis)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Lesions without distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Lesions with distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Staging</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2,3M0N0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4N0M0 ; anyTN1M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>anyTanyNM1</td>
</tr>
</tbody>
</table>

3. Actinic keratosis

Synonyms: Senile keratosis, Solar keratosis

**Outline**

- UV exposure induces keratinocytic atypia, particularly in the basal cell layer. The atypical keratinocytes proliferate in the epidermis. It is the early stage of squamous cell carcinoma in situ.
- Asymptomatic, vaguely margined erythema or keratotic lesions accompanied by scaling and crusting occur in the elderly, on sun-exposed sites of the body.
- Horn-like protrusions (cutaneous horns) form in cases with marked keratinization.
- Cryotherapy, excision and topical anti-cancer agents are the main treatments.

**Clinical features**

A light-pink erythematous plaque several millimeters to 1 cm in diameter occurs on a sun-exposed area of the body, such as the face or dorsal hand. The plaque is covered with scales and crusts. The margin of the plaque is often vague. Keratinization is usually intense. Grayish-white keratotic nodules or horn-like protrusions (cutaneous horns) may form (Fig. 22.8). The skin lesion occurs singly or multiply, most frequently in persons over age 60. Nearly all elderly Caucasians are affected. Actinic keratosis occurs in infancy in patients with xeroderma pigmentosum.

**Pathogenesis**

Epidermal keratinocytes that are damaged by UV proliferate abnormally in the dermis.

**Pathology**

There are three histological types of actinic keratosis (Fig. 22.9, Table 22.4). Malignant changes are localized in the covering epidermis, and follicular and sweat pore regions remain normal. Atypism is found in the lower epidermal basal layer.

**Diagnosis, Differential diagnosis**

Skin biopsy is conducted when it is difficult to differentiate actinic keratosis from seborrheic keratosis and senile lentigo.

<table>
<thead>
<tr>
<th>Table 22. 4 Three histological types of actinic keratosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Hypertrophic actinic keratosis</td>
</tr>
<tr>
<td>Atrophic actinic keratosis</td>
</tr>
<tr>
<td>Bowenoid actinic keratosis</td>
</tr>
</tbody>
</table>

**Fig. 22.8 Actinic keratosis.**

a: Multiple actinic keratosis on the face. b: Erythematous lesion is present. c: Cutaneous horn formed on the preauricular area. d: Actinic keratosis in a patient with xeroderma pigmentosum (group D).
The main treatments are surgical removal, cryotherapy and topical application of anticancer agents such as 5-FU and bleomycin.

**Prognosis**

Some cases progress to squamous cell carcinoma. Aggravation and enlargement of the peripheral erythema and rapid enlargement of ulcers often indicate progression of actinic keratosis.

## 4. Bowen’s disease

### Outline

- It is a squamous cell carcinoma in situ. Highly atypical cells proliferate in all epidermal layers.
- It presents as a sharply-margined plaque, ranging from reddish brown to blackish brown, with a diameter of 1 cm to 10 cm.
- Multiple lesions may be induced by chronic arsenic poisoning.
- It is pathologically characterized by individual cell keratinization and cell clumping.
- Surgical removal and cryotherapy are the main treatments.

### Clinical features

Bowen’s disease occurs solitarily, in the elderly. A round or oval, flatly elevated, relatively sharply edged, infiltrative plaque of several centimeters in diameter, ranging from brown to reddish brown, forms. Underneath the scales and crusts that cover the plaque, red erosion is present (Figs. 22.10-1 and 22.10-2). Small nodules and granuloma may be present.

### Pathology

The pathology of Bowen’s disease corresponds to that of squamous cell carcinoma in situ. Hyperkeratosis, parakeratosis, individual cell keratinization and multinuclear dyskeratotic cells are found in the epidermis. These atypical cells proliferate in all the epidermal layers (Fig. 22.11).

### Pathogenesis

The cause of solitary Bowen’s disease is unknown in many cases. UV exposure and human papillomavirus may induce the disease. Multiple Bowen’s disease is highly associated with arsenic intake. Therefore, history-taking on preexisting conditions such as mass arsenic-poisoning or chronic pesticide poisoning and treatments such as arsenic antisyphilitic therapy are important.
**Diagnosis, Differential diagnosis**

It is differentiated from chronic eczema, psoriasis, actinic keratosis, extramammary Paget’s disease, and superficial type of basal cell carcinoma. Differential diagnosis is made by skin biopsy.

**Treatment**

Surgical removal is the first-line treatment. Application of ointments containing anticancer agents (5-FU and bleomycin) and cryotherapy are also useful.

**Prognosis**

Unless treated, the lesion destroys the basement membranes and progresses to squamous cell carcinoma; it may spread to the lymph nodes.

**5. Erythroplasia of Queyrat**

This is Bowen’s disease on the mucous membranes and at the mucocutaneous junction. Red, characteristically velvety-surfaced plaques appear, mainly on the penis (Fig. 22.12). It may also occur in the female genitalia and oral region. Erythroplasia of Queyrat tends to progress to SCC.

**6. Leukoplakia**

**Definition**

A white keratinous plaque occurs in the mucous membranes and at the mucocutaneous junction. Leukoplakia used to be a diagnostic name for precancerous leukodermas; however, the term has come to include leukodermas caused by various diseases. Leukoplakia may be benign or malignant.

**Clinical features**

The oral cavity and lips are most frequently involved. The tongue, nipples and genital membranes (glans penis, vagina,
perianal region) are affected. Leukoplakia that occurs as a precancerous lesion is slightly infiltrative, smooth-surfaced, keratinous, verrucous, papillary and/or erosive. The epidermis thickens from keratinous proliferation. There is high malignancy when an erythroplasia-like lesion is produced (Fig. 22.13). Men over age 50, especially smokers, are most commonly affected.

**Pathogenesis**

When leukoplakia occurs as a precancerous skin lesion, chronic stimulation such as from smoking may induce cellular atypism, leading to leukoplakia of the mucosa. Benign leukoplakia may be caused by lichen planus, discoid lupus erythematosus, syphilis, candidiasis or external injury.

**Pathology**

In malignant leukoplakia, varying degrees of atypism and dyskeratosis are found in the epidermal cells.

**Diagnosis**

Skin biopsy is necessary to determine whether the lesion is malignant or benign. If there is malignancy, treatment should be done accordingly. If benign, investigation should be made for the underlying disease.

**Treatment**

When there is the possibility of leukoplakia being precancerous, surgical removal, topical 5-FU application, laser therapy or cryotherapy is conducted. Smoking must be stopped.

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**7. Oral florid papillomatosis**

A keratotic or infiltrative plaque varying in shape from papillary to cauliflower-like occurs on the lip or oral mucosa of the elderly. It clinically resembles lip cancer at first sight. The pathogenesis in some cases is thought to be a type of condyloma acuminatum (Chapter 23), with which human papillomavirus is associated. Severe thickening and keratinization of the epidermis are pathologically observed; however, infiltrative proliferation is not present.

**8. Verrucous carcinoma**

This is a squamous cell carcinoma with low-grade malignancy in which elevated keratotic nodules form (Fig. 22.14). Although localized proliferation of the nodules is marked, they rarely metastasize to other organs. Verrucous carcinoma is classified by the affected site into oral mucous verrucous carcinoma, genital verrucous carcinoma and plantar verrucous carcinoma. Surgical removal is the most reliable treatment; the disorder may recur if treated by irradiation or electrosurgery.
9. Keratoacanthoma

**Outline**

- It is a clinically benign tumor that occurs in a hair follicle. Histopathologically, it closely resembles squamous cell carcinoma.
- It appears suddenly and solitarily on the face or dorsal hand, grows rapidly, and forms a dome-shaped, cratered nodule.
- Most cases heal spontaneously in several months. Total resection including skin biopsy is generally performed.
- It is important to differentiate it from squamous cell carcinoma.

**Clinical features**

More than 90% of cases involve the face. Middle-aged and older men are most frequently affected. Keratoacanthoma is solitary in most cases; however, multiple lesions occur in many cases of young persons, and these lesions usually accompany Muir-Torre syndrome.

A small papule occurs and rapidly enlarges in several weeks to a diameter of 1 cm to 2 cm, resulting in formation of a dome-shaped or hemispheric nodule (Figs. 22.15-1 and 22.15-2). The nodule is elastically soft or firm, centrally umbilicated, cratered and accompanied by a red halo. It ranges in color from normal skin to light pink or dark red. After it rapidly enlarges to a certain size, keratinization occurs at the center of the nodule, to form a large keratin plug. Many cases heal spontaneously in several months, with scarring.

**Pathogenesis**

Many years of exposure to sun (UV) or tar, and viral infection or external injury are associated with the occurrence of...
keratoacanthoma.

**Pathology**

Hyperkeratosis is found at the center of the tumor, whose periphery is surrounded by proliferating keratinocytes (Fig. 22.16). The keratinocytes are characterized by clear eosinophilic cytoplasm and atypia. Tumor cells tend not to infiltrate the basement membrane, but lymphocytes and neutrophils infiltrate below the tumor. Keratoacanthoma is thought to be well-differentiated squamous cell carcinoma or pseudocarcinoma.

**Differential diagnosis**

The main distinguishing characteristics of keratoacanthoma are listed in Table 22.5. Skin biopsy is necessary to differentiate keratoacanthoma from squamous cell carcinoma. In squamous cell carcinoma, the border between the edge of the tumor and normal tissue is unclear, and there is asymmetrical morphology and a high tendency of infiltration. Squamous cell carcinoma enlarges far more slowly than keratoacanthoma. Keratoacanthoma is also differentiated from large molluscum contagiosum, in which keratinization does not occur, and from basal cell carcinoma.

**Treatment**

For diagnosis, it is necessary to examine the overall structure of the skin lesion. Total resection of the skin lesion is conducted, which is simultaneously a treatment. If pathological diagnosis is made, follow-ups may be given instead of treatment until the condition resolves. Irradiation, topical application or local injection of steroids or bleomycin ointments, and administration of oral etretinate and cryotherapy are useful.