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presents special issues  
in oncologic pathology.*

## HISTOLOGIC VARIANTS OF SQUAMOUS CELL CARCINOMA OF THE SKIN

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### Introduction

Squamous cell carcinoma (SCC) is the second most common type of skin cancer, with basal cell carcinoma being the most common. However, some argue that an actinic keratosis should be considered as an SCC that is superficial.<sup>1</sup> If so, then SCC could be considered the most common type of skin cancer. The tumor typically appears as a papule or nodule, with varying degrees of hyperkeratosis and ulceration that arises on the sun-exposed skin of elderly patients (Fig 1). The disease has been linked to immunosuppression, arsenic exposure, radiation, chronic ulceration, and human papillomavirus (HPV) infection.<sup>2</sup> The histology reveals a proliferation of atypical keratinocytes that invade the dermis, with areas of detachment from the overlying epidermis. These anastomosing growths of cords and nests are

composed of cells that have a glassy eosinophilic cytoplasm and enlarged nuclei. Mitotic figures, keratin pearls, and dyskeratotic keratinocytes are variably present. On higher power, intercellular bridges may be seen.

While cutaneous SCC is usually easily treatable, it has the potential to recur locally and even metastasize, then leading to significant morbidity and mortality. Therefore, it is important to identify those tumors that are more aggressive and require closer follow-up and possible adjunctive treatments such as micrographic surgery, lymphadenectomy, or radiation therapy. Established prognostic factors include tumor size, depth of invasion, histologic differentiation, anatomic site, perineural invasion, rapid growth, history of previous treatment, host immunosuppression, and etiologic factors such as burn scars, radiation, and chronic

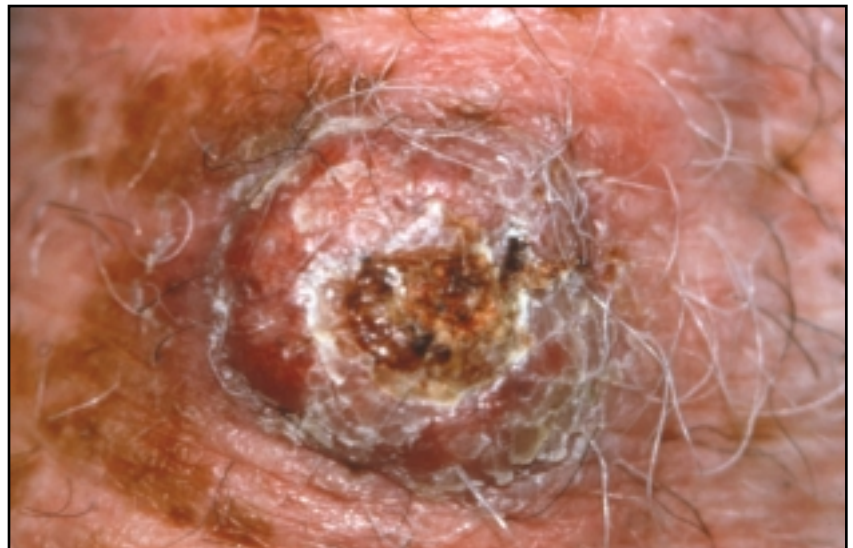


Fig 1. — Squamous cell carcinoma. It typically appears as a papule or nodule, with varying degrees of hyperkeratosis and ulceration that arises on the sun-exposed skin of elderly patients

#### Prognostic Factors for Cutaneous Squamous Cell Carcinoma

Pathology Characteristics:	Clinical Features:
Tumor size	Anatomic site
Histologic differentiation	Growth rate
Depth of invasion	Prior treatment
Perineural invasion	Immunosuppression
Histologic subtype	Etiologic factors
	Burn scars
	Radiation
	Chronic ulceration
	Genetic abnormalities

ulceration (Table).<sup>3</sup> The histologic subtype has also been considered as a factor in determining the prognosis. Several histologic subtypes of SCC are described, including keratoacanthoma, acantholytic, spindle cell, verrucous, clear cell, papillary, signet ring, pigmented, and desmoplastic SCC. These variants of SCC are reviewed for their clinical and histologic features and the risk of recurrence and metastasis.

## Bowen's Disease

Bowen's disease, also known as SCC in situ, was first described by John Bowen in 1912. It presents as a slow-growing, sharply demarcated erythematous scaly patch. Hyperkeratosis, crusting, fissuring, or pigmentation may be associated. Although Bowen's disease is usually seen in sites of chronic sun exposure, it can occur on any mucocutaneous surface. Tumor size ranges from a few millimeters to several centimeters.<sup>4</sup> It is common in elderly patients, and the male-to-female ratio is approximately equal. When it occurs on the penis, it is referred to as erythroplasia of

Queyrat, a disease that tends to occur in men who are uncircumcised and appears as solitary or multiple red, smooth, velvety plaques.<sup>2</sup>

Bowen's disease is characterized histologically by hyperkeratosis, parakeratosis, and acanthosis with thickened and elongated rete ridges. Scattered atypical cells and frequent mitoses are present. The keratinocytes show loss of maturity and polarity, giving the epidermis a disordered or "wind-blown" appearance. The dermal epidermal junction is intact, which distinguishes Bowen's disease from invasive SCC. There may be a moderate inflammatory infiltrate of lymphocytes and histiocytes.<sup>4</sup>

It has been previously reported that Bowen's disease may be associated with internal malignancy; however, recent studies have failed to confirm this.<sup>4</sup>

Treatment by excision or destruction is recommended. Theoretically, there is no risk of metastasis with Bowen's disease because it is confined to the epidermis. If not treated, however, it could progress to invasive SCC, which then carries a risk of metastasis.<sup>2</sup>

## Keratoacanthomas

Keratoacanthomas (KAs) were first described in 1889 by Jonathan Hutchinson as crateriform ulcers of the face. They have also been referred to by other terms such as molluscum sebaceum, molluscum pseudocarcinomatousum, self-healing primary squamous carcinoma, and keratocarcinoma.<sup>5</sup> They are clinically distinctive, rapidly growing, cutaneous tumors that generally present as crateriform nodules in elderly, fair-skinned individuals (Fig 2). The tumor most commonly appears on sun-exposed skin but may occur anywhere on the body. In addition to ultraviolet exposure, KAs have also been associated with chronic skin conditions that produce scarring such as stasis dermatitis, lichen planus, discoid lupus erythematosus, and thermal burns.<sup>6</sup>

The three clinical stages of KAs are proliferative, maturation, and involution. The proliferative stage is noted for the sudden appearance of an erythematous to flesh-colored



Fig 2. — Keratoacanthoma. This cutaneous tumor is a clinically distinctive, rapidly growing, cutaneous tumor that generally presents as a crateriform nodule in elderly, fair-skinned individuals.

papule with fine telangiectasias. The lesion enlarges rapidly, achieving a diameter of up to 2 cm or more. As the KA progresses through the maturation stage, it becomes dome-shaped with a central keratinous core. It typically lacks induration or fixation to underlying tissue. Within a few months, involution may take place, eventually resulting in a depressed hypopigmented scar.<sup>5</sup>

Histologically, in the proliferative stage, the lesion appears as a well-circumscribed, keratin-filled invagination of the epidermis with hyperkeratosis and acanthosis. Epidermal lobules and strands composed of atypical squamous cells extend into the dermis. There usually is a surrounding mixed inflammatory infiltrate. Atypical mitotic figures, perineural invasion, and intravascular extension may be present. As the tumor progresses into the maturation stage, the atypia becomes less promi-

nent. The fully developed lesion is volcano-shaped with buttresses of normal epidermis. Within the volcano is abundant hyaline keratin, which has a “glassy” appearance. Atypical squamous proliferations may be seen at the base of the crater and extending into the crater (Fig 3). During the involution stage, the lesion has a dense lichenoid infiltrate with multinucleated histiocytes, granulation tissue, and fibrosis, and it may eventually result in an atrophic scar.<sup>5</sup>

KAs can be difficult to distinguish histologically from conventional SCCs. This has prompted some to consider KAs and SCCs to be the same. Clinically, they are differentiated by their history of rapid growth and their volcano shape, yet histologically, there are too many features that overlap with SCC to allow reliable separation.

Although KAs were once considered benign based on behavior,

it is now believed that they should be regarded as well-differentiated variants of SCC that are capable of spontaneous regression. Some KAs have displayed aggressive biologic behavior that has led to metastases and even death.<sup>7,8</sup> Because of this potential for local recurrence and metastasis, treatment by excision or destruction is recommended.

## Acantholytic Squamous Cell Carcinoma

Acantholytic SCC (ASCC) may also be referred to as adenoid SCC, adenoacanthoma, or pseudoglandular SCC. This variant was initially described in 1947 as a tumor composed of both solid and gland-like epithelial proliferations extending into the dermis, which was labeled adenoacanthoma of sweat glands. Most authors now regard ASCC as a variant of SCC rather than a sweat gland tumor.<sup>9</sup> It usually has a typical SCC pattern in combination with glandular formations, dyskeratotic cells, and acantholysis.

Clinically, this tumor is most often seen in the sun-exposed areas of the head and neck of elderly patients, and it most likely arises from acantholytic actinic keratoses. There have been reports, however, of this tumor occurring in sun-protected areas such as the dorsum of the foot.<sup>9</sup> There is a striking male predominance, with only three women affected in a total of 155 patients in a review by Johnson and Helwig,<sup>10</sup> and three women out of 49 patients in a review by Nappi et al.<sup>11</sup> ASCC may appear as a flesh-colored, pink, or brown nod-

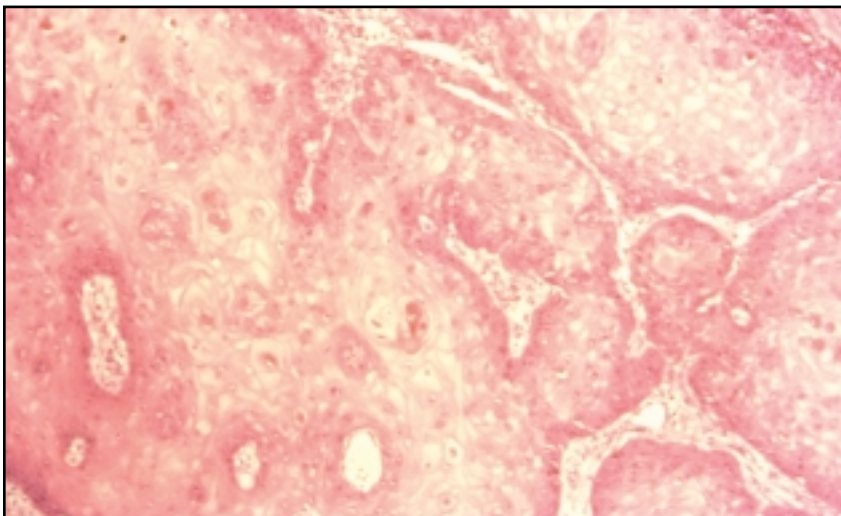


Fig 3. — Atypical squamous proliferations of keratoacanthoma. Atypical squamous proliferations may be seen at the base of the crater and extending into the crater.

ule. Crusting, scaling, or ulceration may be present.

Histologically, the tumor is composed of strands and islands of atypical epithelial cells extending into the dermis. Connection to the overlying epidermis is seen in most cases, which may show hyperkeratosis and parakeratosis. However, this connection may be only focal or, in some cases, absent. Many of the tumor strands may show tubular and alveolar formations, which are referred to as pseudoglandular appendages. These spaces contain acantholytic cells that result from loss of cohesion of the tumor cells (Fig 4). These acantholytic cells may appear extremely bizarre, large, or multinucleated. Mitotic figures are variably present. Classic SCC may also show cleft formation with dyskeratosis and acantholysis, but it does not have a definite wall or cohesive layer of cells surrounding the acantholytic cells, as seen in ASCC.<sup>10</sup>

ASCC may be mistaken for eccrine adenocarcinomas, metastatic adenocarcinomas, or epithelioid angiosarcomas. In the eccrine adenocarcinoma, the glandular spaces are lined with periodic acid-Schiff (PAS)-positive cells, whereas in ASCC, the cells are PAS-negative. Also, ASCC lacks the production of carcinoembryonic antigen, S100 protein, and amylase, which can be seen in glandular malignancies.<sup>11</sup> In epithelioid angiosarcoma, the vascular spaces contain red blood cells, as opposed to the atypical keratinocytes seen in acantholytic SCC. ASCC may also contain red blood cells within

the pseudoglandular spaces. In these cases, immunohistochemical stains may be required. Angiosarcomas are typically positive for vimentin and CD-34, whereas ASCC is positive for cytokeratin (CK) and epithelial membrane antigen (EMA).

It was initially thought that ASCC had less potential to metastasize to lymph nodes than did de novo SCC. In a 1966 review of 155 patients with 213 lesions,<sup>10</sup> only three patients died of metastatic disease and two patients died of local invasion. One of the deaths due to local invasion involved a patient who refused treatment. In a review of 20 patients in 1972,<sup>12</sup> no patients were noted to have lymph node metastases, but three patients died of local intracranial extension of tumor. This low propensity to metastasize was disputed in 1989 by Nappi et al.<sup>11</sup> In

their review of 36 patients, 11 patients had local recurrence, five had visceral metastases, and two died of local intracranial extension of tumor. Another review by Nappi and colleagues<sup>13</sup> in 1992 noted that three out of six patients with ASCC died of lymph node metastasis. However, two of these were immunocompromised. In a review by Toyama et al<sup>9</sup> in 1995, one out of four patients died of lymph node metastases. The lack of data regarding lesion sizes and the circumstances of the patients in several of these reviews makes it difficult to adequately assess the metastatic potential of ASCC. In a more recent review of 18 patients by Petter and Haustein<sup>14</sup> in 1998, only one patient developed a local recurrence. Although the literature has been conflicting, we believe that the malignant potential of ASCC is no higher than that of a typical invasive SCC.

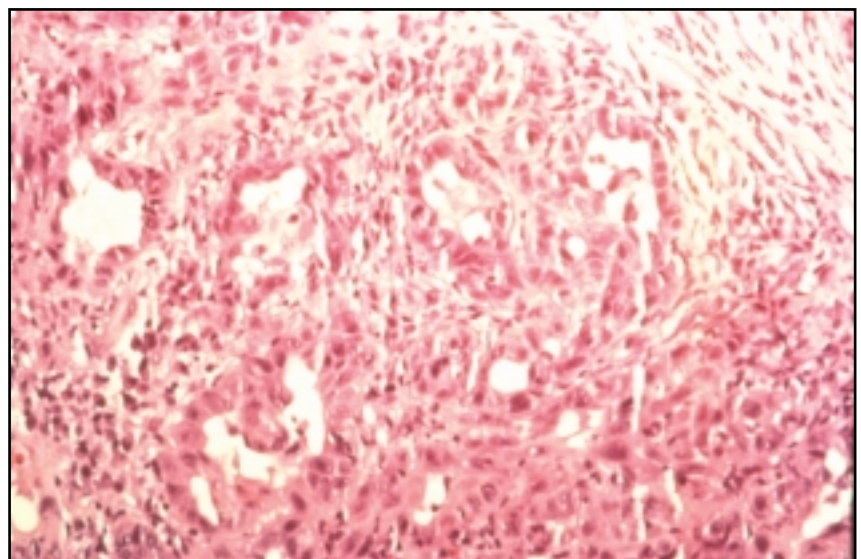


Fig 4. — Acantholytic squamous cell carcinoma. Many of the tumor strands may show tubular and alveolar formations, which are referred to as pseudoglandular appendages. These spaces contain acantholytic cells that result from loss of cohesion of the tumor cells.

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## Spindle Cell Squamous Cell Carcinoma

Spindle cell SCC is a rare variant of SCC. Clinically, it may appear as an exophytic tumor or an ulcerated mass on the sun-exposed skin of elderly patients. Histologically, it is composed of atypical spindle cells arranged in a whorled pattern. Unlike conventional SCC, the tumor cells infiltrate the dermis singly, without the formation of nests and cords. There may or may not be connection to the overlying epidermis. Mitoses and bizarre pleomorphic giant cells may be frequently seen. Deep infiltration of the dermis, subcutis, and underlying fascia is common. Spindle cell SCC may be difficult to distinguish from an atypical fibroxanthoma or a desmoplastic melanoma, in which case immunohistochemistry is required. Spindle cell SCC will stain positive for high-molecular-weight CK and EMA. Atypical fibroxanthomas will stain positive for vimentin, and spindle cell melanomas will stain positive for S100 protein. Some poorly differentiated spindle cell SCCs may show loss of cytokeratin expression and aberrant vimentin expression, making the diagnosis even more challenging.<sup>15</sup> Electron microscopy can be used in addition to immunohistochemistry to confirm the diagnosis. The presence of tonofilaments and desmosomes confirms an epithelial origin.<sup>16</sup> Poorly differentiated spindle cell SCC, however, may not always have evidence of tonofilaments and desmosomes, making them indistinguishable from sarcomas.

Spindle cell SCC was initially reported by Martin and Stewart in 1935.<sup>17</sup> It was believed that previous radiation was the most important cause, as six of the eight patients reported had a history of radiation. It was also thought to be an aggressive form of SCC, as four of these eight patients died of the cancer. This was disputed in 1950 in a report of five cases by Strauss<sup>18</sup> in which none of the patients had a history of radiation exposure. In the follow-up of these patients, there were no reports of recurrence or metastasis. In 1972, Smith<sup>19</sup> proposed that when spindle cell SCCs arise in a site of previous radiation, they tend to have a more aggressive course, as would be expected. When they arise *de novo*, Smith proposed that these lesions do not exhibit a more aggressive behavior than conventional SCC. Spindle cell SCC has also been reported in renal transplant patients, in which one of four patients developed metastatic disease.<sup>15</sup> Unfortunately, no large studies have been conducted regarding the prognosis of spindle cell SCC, especially comparing *de novo* lesions with radiation-associated lesions.

## Verrucous Carcinoma

Verrucous carcinoma is a low-grade variant of SCC with little potential for distant metastases. However, it has the potential to cause local destruction. The term “verrucous carcinoma” was first used by Ackerman<sup>20</sup> in 1948 to describe a carcinoma of the oral cavity. In 1954, Aird et al<sup>21</sup> de-

scribed a histologically similar tumor on the plantar surface, which they named carcinoma cuniculatum. A similar tumor of the anogenital region, named the giant condyloma of Buschke and Löwenstein,<sup>22</sup> had already been described in 1925. In 1960, Rock and Fisher,<sup>23</sup> probably not aware of the already-described verrucous carcinoma by Ackerman, suggested the term oral florid papillomatosis to describe vegetating verrucous lesions in the mouth that simulated carcinoma. It is now thought that all three tumors — oral florid papillomatosis, giant condyloma, and carcinoma cuniculatum — represent verrucous carcinomas. In addition to occurring in the oral cavity, genital area, and the plantar surface, verrucous carcinoma may occur anywhere on the skin.

Although the pathogenesis of verrucous carcinoma remains unknown, HPV, chronic irritation, and chemicals have been implicated. The diagnosis of this type of SCC may be particularly challenging due to its bland histologic features. A superficial biopsy is usually not sufficient to distinguish this tumor from verruca vulgaris, KAs, and pseudoepitheliomatous hyperplasia. Therefore, obtaining a deep incisional biopsy is recommended.

## Epithelioma Cuniculatum

Epithelioma cuniculatum, also referred to as carcinoma cuniculatum, was first described by Aird et al in 1954.<sup>21</sup> The word epithelioma means “tumor of the epithelium” and cuniculate refers to crypt-like spaces seen on histology that

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resemble rabbit burrows. Since its original description, more than 100 cases have been reported with this variant of SCC. It is now thought to represent a variant of verrucous carcinoma localized to the plantar surface. Trauma, chronic irritation, and HPV infection have been implicated as possible triggering factors.<sup>24</sup>

Epithelioma cuniculatum is often seen in older white men. The mean age of presentation is 52-60 years, with a range of 23-84 years.<sup>25</sup> It tends to occur most commonly on the ball of the sole (53%), followed by the toes (21%) and the heel (16%).<sup>24</sup> Initially, the tumor may resemble a plantar wart, but it may slowly progress to form a bulky, exophytic mass. It may become ulcerated and develop numerous sinuses from which a foul-smelling purulent keratinous debris can be expressed. It has often been described as a "squashy" mass, with the consistency of an overripe orange.<sup>25</sup> The tumor can be deforming and painful, leading to difficulty with ambulation.

On histology, it has both an endophytic and exophytic growth pattern. The cells are well differentiated, and pronounced hyperkeratosis and papillomatosis are usually present. Tumor strands may extend deep into the dermis and subcutis, forming keratin-filled intraepidermal abscesses and sinuses with the surface. These sinus tracts are the "rabbit-burrow-like spaces" from which epithelioma cuniculatum derives its name. The surrounding stroma may demonstrate an infiltrate of lymphocytes, histiocytes,

eosinophils, and plasma cells. On close examination, atypia with nuclear enlargement, hyperchromasia, and mitoses may be evident.<sup>24</sup> The major differential diagnoses include pseudoepitheliomatous hyperplasia and giant plantar warts.

Although it is not considered an aggressive form of SCC, there have been reports of metastases to skin and lymph nodes. In a study of 46 cases by Kao and colleagues,<sup>24</sup> follow-up data were obtained on 26 patients. Three patients had local recurrence and three had distant metastases. None of the patients at that time had disseminated disease or died of metastatic disease.

## Giant Condyloma of Buschke and Löwenstein

Giant condyloma of Buschke and Löwenstein was first described in 1896.<sup>26</sup> It was further studied in 1925 by Buschke and Löwenstein,<sup>22</sup> at which time it was given its name. In 1948, Ackerman<sup>20</sup> described the term "verrucous carcinoma," which occurred in the oral cavity. It is now recognized that giant condyloma of Buschke and Löwenstein is a verrucous carcinoma localized to the anogenital region. It is also referred to as the Buschke-Löwenstein tumor, verrucous carcinoma of anogenital mucosa, or carcinoma-like condyloma.<sup>27</sup>

The classic Buschke-Löwenstein tumor occurs as an exophytic, fungating, cauliflower-like mass on the penis. There may be ulceration or fistulous tracts with purulent, foul-smelling drainage. The most com-

mon site of involvement is the glans penis and prepuce, but this tumor may occur on any ano-urogenital surface. It is most frequently seen in middle-aged, uncircumcised men, with two thirds of cases occurring in men younger than 50 years of age.<sup>25</sup> It has also been reported to occur in women on the vulva, vagina, or cervix.<sup>28</sup> Swollen, tender lymph nodes commonly occur due to secondary bacterial infection. There is a strong association between the Buschke-Löwenstein tumor and HPV types 6 and 11. Other risk factors include poor hygiene and lack of circumcision.<sup>29</sup>

A deep biopsy is required to confirm the diagnosis. Marked papillomatosis and acanthosis with hyperkeratosis and parakeratosis are present. A prominent granular layer with vacuolated cells similar to koilocytes may be seen. Blunt-shaped projections extend into the dermis, some forming sinuses with keratin-filled cysts. A dense, inflammatory infiltrate is often present. Contrary to invasive SCC, there is little atypia, and there are no infiltrating nests of squamous cells. Although this tumor rarely metastasizes, it can cause significant local destruction. It tends to have a downward growth pattern and may compress the corpus cavernosum and involve the urethra.<sup>27</sup>

## Verrucous Carcinoma of the Oral Cavity

Verrucous carcinoma of the oral cavity was first reported by Ackerman<sup>20</sup> in 1948. In 1960, Rock and Fisher<sup>23</sup> described a similar

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lesion, which they named oral florid papillomatosis. It is now agreed that oral florid papillomatosis merely represents a verrucous carcinoma of the oral cavity. It has also been referred to as Ackerman tumor or verrucous carcinoma of Ackerman.

Clinically, oral florid papillomatosis is most commonly seen in elderly white men. In its early stages, it appears as a white keratotic patch. Later, it appears as a soft, rubbery, papillary growth that may have ulceration. It occurs most commonly on the buccal mucosa and the gingiva.<sup>30</sup> Patients may have lymphadenopathy due to secondary infection. There is a definite association with tobacco use, including smoking, snuff dipping, and betel chewing, all of which may cause leukoplakia. The tumor is most frequently preceded by leukoplakia, which was noted in up to 57% of patients in one series. It may also be preceded by oral lichen planus, chronic candidiasis, and chronic lupus erythematosus.<sup>30</sup>

Histology reveals a sharply circumscribed tumor, with marked papillomatosis and overlying hyperkeratosis. Broad bulbous acanthotic projections of epidermis may extend deep into the stroma. An associated dense inflammatory cell infiltrate is often present. As with other forms of verrucous carcinoma, little atypia is present in most cases.

Although distant metastases are rare, local destruction may occur, with invasion into bone. The treatment of choice is surgical exci-

sion. Radiation therapy should be avoided due to the risk of anaplastic transformation to a more aggressive form of SCC.<sup>31</sup>

## Clear Cell Squamous Cell Carcinoma

Clear cell carcinoma is also referred to as hydropic SCC. It was first described by Kuo<sup>32</sup> in 1980 as a variant of SCC with extensive hydropic change. The hydropic degeneration of neoplastic cells and the accumulation of intracellular fluid, not the accumulation of glycogen, lipid, or mucin, results in its clear cell appearance. Clear cell carcinoma occurs most commonly in elderly white men with a history of excessive sun exposure. All cases have occurred in the head and neck region, with the mandible being the most common site. Clinically, it appears as a nodule or mass that may occasionally be ulcerated. Of the six cases reported, four were noted to have rapid growth.

Kuo<sup>32</sup> further classified the six cases of clear cell carcinoma into three major histologic types: keratinizing (type I), nonkeratinizing (type II), and pleomorphic (type III). Type I is characterized by sheets or islands of tumor cells in a fibrotic stroma, with a sparse lymphocytic infiltrate. The tumor cells appear clear, with peripherally displaced nuclei, and may be indistinguishable from adipose cells. Some cells may also appear to have a "bubbled" cytoplasm, resembling sebaceous cells. Distinguishing features include foci of keratiniza-

tion and keratin pearls. Type II is characterized by parallel or anastomosing cords of tumor cells in a compressed fibrotic stroma with a dense, inflammatory infiltrate composed of plasma cells and lymphocytes. Central necrosis may be evident within tumor cords. The tumor cells appear to have central nuclei with finely reticulated clear cytoplasm. Unlike type I, this variant does not demonstrate evidence of keratinization. Type III demonstrates marked pleomorphism with extensive vascular and perineural invasion. Foci of squamous differentiation and microcysts with acantholytic tumor cells may be seen. In all three types, none has evidence of either glycogen or mucin in tumor cells.<sup>32</sup>

This clear cell variant of SCC may be easily mistaken histologically for a sebaceous neoplasm. Distinguishing features, however, include evidence of squamous differentiation and a negative fat stain using Oil Red O. It may also appear similar to other clear cell tumors, including clear cell acanthoma, clear cell hidradenoma, clear cell hidradenocarcinoma, tricholemmoma, metastatic renal cell carcinoma, pilar tumor, balloon cell nevus, and balloon cell melanoma. Clear cell acanthoma, clear cell hidradenoma, clear cell hidradenocarcinoma, tricholemmoma, and metastatic renal cell carcinoma have a high content of cytoplasmic glycogen, which is not seen in the clear cell variant of SCC. Pilar tumors with clear cell change demonstrate marginated nuclei simulating the lower hair sheath cells and have glassy keratinization surrounded by a vitreous

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membrane-like stroma. Balloon cell nevus and melanoma usually demonstrate nests of melanocytes and pigment production.

It is difficult to determine the prognosis of clear cell SCC based on the few cases that have been reported in the literature. Of the six patients reported, one died of metastatic disease, one died post-operatively, and one was noted to have recurrence after 3 months.

## Papillary Squamous Cell Carcinoma

In 1990, Landman and colleagues<sup>33</sup> reported two patients with an unusual exophytic papillary growth pattern of SCC. They considered these tumors to be histologically distinct from verrucous carcinomas and referred to them as cutaneous papillary SCC. Both tumors occurred in elderly women and were located on the face. They presented as red nodules or tumors that clinically resembled SCC or pyogenic granuloma.

Histologically, they appear as exophytic, pedunculated masses with large papillary fronds permeated by fibrovascular cores. The cells adjacent to the stromal core are smaller with dark basophilic cytoplasm. The cells closer to the external surface show either clear or abundant pink cytoplasm. Nuclear atypia and mitotic figures can be readily seen. There may be only focal areas of invasion of the stroma with the tumor cells. A dense infiltrate of lymphocytes, plasma cells, and neutrophils was

noted to permeate the stroma. In both reported cases, staining for HPV was negative. Unlike verrucous carcinoma, there was no evidence of downward growth of irregular strands of squamous cells infiltrating the dermis. In addition, the high degree of atypia and number of mitotic figures seen in these cases is not typical for verrucous carcinoma. Verrucous Bowen's disease may also demonstrate papillomatous projections; however, these do not have a fibrovascular core.

Both cases of papillary SCC were treated by electrodesiccation and curettage, and no evidence of recurrence was seen at a follow-up of 18 months. More cases are needed to adequately determine the biologic behavior of this variant of SCC.

## Signet Ring Squamous Cell Carcinoma

A case of signet ring SCC was first described by Cramer and Heggeness<sup>34</sup> in 1989. A second case was reported by McKinley et al<sup>35</sup> in 1998. Signet ring cells typically have nuclear displacement and compression by cytoplasmic contents. They have been described in a variety of tumors, including adenocarcinomas, lymphomas, melanomas, and sarcomas.

Clinically, the lesions appeared as an ulcerated plaque or nodule. The histology demonstrated intra-epidermal and invasive dermal cells characterized by a signet ring appearance. The diagnosis of SCC

could be easily overlooked in this situation. Fortunately, in one case, the tumor arose in a site previously diagnosed as SCC, and in the other case, there were foci of typical SCC. This prompted the inclusion of keratin stains, which were positive.<sup>34,35</sup>

With only two cases having been reported, it is impossible to determine its biologic behavior. In one case, the tumor behaved in an aggressive manner with extensive local invasion and lymph node metastasis, leading to death.<sup>34</sup> Further cases are needed to determine its true biologic behavior.

## Pigmented Squamous Cell Carcinoma

Only a few reports of infiltrating pigmented SCC of the skin (IPSCC) are available. A report by Jurado and colleagues<sup>36</sup> in 1998 describes two cases of IPSCC. Both occurred in elderly men and were located on the face. In one case, the tumor had been slowly growing over a period of several years, and clinically it resembled a melanoma. The other case resembled a pigmented basal cell carcinoma (BCC). Both tumors were excised, with no evidence of recurrence or metastasis after a 4-year follow-up. A more recent report by Morgan et al<sup>37</sup> evaluated five cases of IPSCC. These tumors all presented as rapidly growing crusted papules on actinic damaged skin of the face. After excision, an average follow-up of 4 years failed to demonstrate any local recurrence or metastasis.

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The histology of these tumors demonstrates a mixture of keratinized squamous cells and melanin-producing dendritic melanocytes. The squamous cells stain positively with epithelial membrane antigen and both low- and high-molecular keratin. Melanin can be confirmed with a Fontana-Masson stain. The dendritic cells are reactive with vimentin, S100 protein, and HMB45. Some of the neoplastic squamous cells have been reported to demonstrate focal positivity for S100 and HMB45, which may be due to transference of antigen from the dendritic melanocytes to the neoplastic cells.

The differential diagnosis of IPSCC includes pigmented BCC, pilomatrixoma, dermal squamo-melanocytic tumor, and melanoma with pseudoepitheliomatous hyperplasia.<sup>37</sup> Pigmented BCC can be distinguished by the presence of peripherally palisading basaloid cells, limited keratinization, and negative staining for epithelial membrane antigen and high-molecular-weight keratins. Pilomatrixoma has characteristic "ghost cells" and also stains negatively for epithelial membrane antigen and high-molecular-weight keratins. Melanoma with pseudoepitheliomatous hyperplasia has benign-appearing epithelial cells with atypical-appearing melanocytes, which contrasts to the atypical squamous cells with banal-appearing melanocytes in IPSCC. The dermal squamo-melanocytic tumor can be distinguished by the presence of nonkeratinizing atypical nonpigmented cells that are negative for both S100 and keratin antibodies.<sup>37</sup>

Due to the small number of reported cases, it is difficult to make any definitive conclusions regarding the malignant potential of IPSCC.

### Desmoplastic Squamous Cell Carcinoma

Desmoplastic SCC is a new variant of SCC that was first described by Haneke<sup>38</sup> in 1989. Desmoplastic SCCs commonly occur on sun-exposed areas of the head and neck, with a high proportion of lesions being found on the ear. The histology demonstrates a prominent trabecular growth pattern, narrow columns of atypical epithelial cells, and a marked desmoplastic stromal reaction. A study done by Breuninger and colleagues<sup>39</sup> in 1997 reviewed 44 cases of desmoplastic SCC that were identified in a prospective review of 594 SCCs. All of the lesions were treated with standard micrographic surgery. The median follow-up for these patients was 5 years. The desmoplastic SCCs were found to metastasize six times more often than common SCCs (22.7% vs 3.8%) and have local recurrences 10 times more often than common SCCs (27.3% vs 2.6%). This poorer prognosis cannot be due to advanced tumor invasion because the desmoplastic SCCs were found to metastasize more often than typical SCCs of comparable tumor thickness. These authors recommended more aggressive treatment for desmoplastic SCCs, including wider excision margins, close follow-up with lymph node examination, and lymph node dissection for lesions deeper than 5 mm.

### Conclusions

Squamous cell carcinoma is a common tumor of the skin with potential for local recurrence and metastasis. It is important to determine which tumors are high risk in order to determine the appropriate treatments. Higher-risk tumors may require micrographic surgery, lymph node dissection, or even adjunctive radiation treatment. The histologic subtype has been considered as a possible variable in determining the prognosis of cutaneous SCC. Bowen's disease, KAs, and verrucous carcinomas appear to have a lower malignant potential than typical invasive SCCs. Several conflicting reports regarding the prognosis of acantholytic SCC have been published; however, a more recent report has not confirmed the higher malignant potential that was once suspected. Although some believe that spindle cell carcinoma may be more aggressive than conventional SCC, most reports of recurrence and metastasis occurred in patients with a previous history of radiation therapy or immunosuppression. It appears that spindle cell SCC arising de novo does not have a higher malignant potential. Due to the relatively small number of reported cases of clear cell, papillary, signet ring, and pigmented SCCs, it is difficult to make any definitive statements regarding their prognosis compared to typical invasive SCC. A preliminary review of the desmoplastic variant of SCC indicates a higher malignant potential than typical invasive SCC.

Other clinical and histologic factors that have been associated

with a higher risk of local recurrence and metastasis include tumor size, depth of invasion, histologic differentiation, anatomic site, perineural invasion, rapid growth, history of previous treatment, host immunosuppression, and etiologic factors such as scar, chronic ulceration, or radiation.<sup>3</sup> In an extensive review in 1992, Rowe et al<sup>3</sup> noted that it is difficult to assess the relation between each of the prognostic factors because each factor is uncontrolled and overlaps with so many other factors. Large randomized, prospective trials are needed to determine the relative importance of each of the prognostic factors for SCC.

## References

1. Heaphy MR, Ackerman AB Jr. The nature of solar keratosis: a critical review in historical perspective. *J Am Acad Dermatol.* 2000;43:138-150.
2. Johnson TM, Rowe DE, Nelson BR, et al. Squamous cell carcinoma of the skin. *J Am Acad Dermatol.* 1992;26:467-484.
3. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol.* 1992;26:976-990.
4. Lee MM, Wick MM. Bowen's disease. *Clin Dermatol.* 1993;11:43-46.
5. Schwartz RA. Keratoacanthoma. *J Am Acad Dermatol.* 1994;30:1-19.
6. Skidmore RA Jr, Flowers FP. Non-melanoma skin cancer. *Med Clin North Am.* 1998;82:1309-1323.
7. Hodak E, Jones RE, Ackerman AB. Solitary keratoacanthoma is a squamous-cell carcinoma: three examples with metastases. *Am J Dermatopathol.* 1993;15:332-342.
8. Requena L, Romero E, Sanchez M, et al. Aggressive keratoacanthoma of the eyelid: "malignant" keratoacanthoma or squamous cell carcinoma? *J Dermatol Surg Oncol.* 1990;16:564-568.
9. Toyama K, Hashimoto-Kumasaka K, Tagami H. Acantholytic squamous cell carcinoma involving the dorsum of the foot of elderly Japanese: clinical and light microscopic observations in five patients. *Br J Dermatol.* 1995;133:141-142.
10. Johnson WC, Helwig EB. Adenoid squamous cell carcinoma (adenocanthoma). A clinicopathologic study of 155 patients. *Cancer.* 1966;19:1639-1650.
11. Nappi O, Pettinato G, Wick MR. Adenoid (acantholytic) squamous cell carcinoma of the skin. *J Cutan Pathol.* 1989;16:114-121.
12. Carpeto FJ, Garcia-Perez A. Adenocanthoma: a review of 20 cases, compared with the literature. *Dermatologica.* 1972;145:269-279.
13. Nappi O, Wick MR, Pettinato G, et al. Pseudovascular adenoid squamous cell carcinoma of the skin. A neoplasm that may be mistaken for angiosarcoma. *Am J Surg Pathol.* 1992;16:429-438.
14. Petter G, Hausteiner UE. Squamous cell carcinoma of the skin: histopathological features and their significance for the clinical outcome. *J Eur Acad Dermatol Venereol.* 1998;11:37-44.
15. Harwood CA, Proby CM, Leigh IM, et al. Aggressive spindle cell squamous cell carcinoma in renal transplant recipients. *Br J Dermatol.* 1996;135:23.
16. Feldman PS, Barr RJ. Ultrastructure of spindle cell squamous carcinoma. *J Cutan Pathol.* 1976;3:17-24.
17. Martin HE, Stewart FW. Spindle cell epidermoid carcinoma. *Am J Cancer.* 1935;24:273-297.
18. Strauss MJ. Spindle cell epidermoid carcinoma: report of five cases in patients who had never been exposed to roentgen rays. *Arch Dermatol Syphilol.* 1950;61:633-647.
19. Smith JL. Spindle cell squamous carcinoma. In: Graham JH, Johnson WC, Helwig EB, eds. *Dermal Pathology.* Hagerstown, Md: Harper and Row; 1972:631-635.
20. Ackerman LV. Verrucous carcinoma of the oral cavity. *Surgery.* 1948;23:670-678.
21. Aird I, Johnson HD, Lennox B, et al. Epithelioma cuniculatum: a variety of squamous carcinoma peculiar to the foot. *Br J Surg.* 1954;42:245-250.
22. Buschke A, Löwenstein L. Über carcinomähnliche condylomata acuminata des penis. *Klin Wochenschr.* 1925;4:1726-1728.
23. Rock JA, Fisher ER. Florid papillomatosis of the oral cavity and larynx. *Arch Otolaryngol.* 1960;72:593-598.
24. Kao GF, Graham JH, Helwig EB. Carcinoma cuniculatum (verrucous carcinoma of the skin): a clinicopathologic study of 46 cases with ultrastructural observations. *Cancer.* 1982;49:2395-2403.
25. Schwartz RA. Verrucous carcinoma of the skin and mucosa. *J Am Acad Dermatol.* 1995;32:1-21.
26. Buschke A. Condyloma acuminata. In: Neisser A, ed. *Stereoscopischer Medizinischer Atlas.* Kassel, Germany: T Fisher; 1896. Plate 61.
27. Schwartz RA. Buschke-Löwenstein tumor: verrucous carcinoma of the penis. *J Am Acad Dermatol.* 1990;23:723-727.
28. Crowther ME, Lowe DG, Shepherd JH. Verrucous carcinoma of the female genital tract: a review. *Obstet Gynecol Surv.* 1988;43:263-280.
29. Sherman RN, Fung HK, Flynn KJ. Verrucous carcinoma (Buschke-Löwenstein tumor). *Int J Dermatol.* 1991;30:730-733.
30. Grinspan D, Abulafia J. Oral florid papillomatosis (verrucous carcinoma). *Int J Dermatol.* 1979;18:608-620.
31. Perez CA, Kraus FT, Evans JC, et al. Anaplastic transformation in verrucous carcinoma of the oral cavity after radiation therapy. *Radiology.* 1966;86:108-115.
32. Kuo T. Clear cell carcinoma of the skin: a variant of the squamous cell carcinoma that stimulates sebaceous carcinoma. *Am J Surg Pathol.* 1980;4:573-583.
33. Landman G, Taylor RM, Friedman KJ. Cutaneous papillary squamous cell carcinoma: a report of two cases. *J Cutan Pathol.* 1990;17:105-110.
34. Cramer SE, Heggeness LM. Signet-ring squamous cell carcinoma. *Am J Clin Pathol.* 1989;91:488-491.
35. McKinley E, Valles R, Bang R, et al. Signet-ring squamous cell carcinoma: a case report. *J Cutan Pathol.* 1998;25:176-181.
36. Jurado I, Saez A, Luelmo J, et al. Pigmented squamous cell carcinoma of the skin: report of two cases and review of the literature. *Am J Dermatopathol.* 1998;20:578-581.
37. Morgan MB, Lima-Maribona J, Miller RA, et al. Pigmented squamous cell carcinoma of the skin: morphologic and immunohistochemical study of five cases. *J Cutan Pathol.* 2000;27:381-386.
38. Haneke E. Histologische Varianten des plattenepithelkarzinoms der Haut und ihre Dignität. In: Breuninger H, Rassner G, eds. *Operationsplanung und Erfolgskontrolle.* Berlin, Germany: Springer Verlag; 1989:79-85.
39. Breuninger H, Schaumburg-Lever G, Holzschuh J, et al. Desmoplastic squamous cell carcinoma of skin and vermilion surface: a highly malignant subtype of skin cancer. *Cancer.* 1997;79:915-919.