Squamous cell carcinoma (in situ and invasive): Review

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Squamous cell carcinoma of the skin

Squamous cell carcinoma (SCC) is the second most common (20%) malignant tumor of the skin after basal cell carcinoma (80%).

Most squamous cell carcinoma occurs on the sun-exposed skin as non-invasive squamous cell carcinoma in-situ that may eventually progress to invasive squamous cell carcinoma.

Actinic keratosis of the skin is a precancerous lesion that may progress to SCC.

Most Squamous cell carcinomas of the skin are the result of ultraviolet ray exposure from sun or indoor tanning just like actinic keratosis. Most common locations are face, ears, neck, hands and arms. But it can develop in the skin in any part of the body.

Other than chronic sun exposure, additional risk factors include: Fair skin, light hair, people who gets sun burn easily, older age (>50 yrs), and male sex (double the risk over female).
Squamous cell carcinoma of the skin is a malignant tumor arising from keratinocytes.

Q. From which layer? Basal, spinous, granular, corneal?
- Basal layer. These small cuboidal keratinocytes are the proliferative cells that mature into the keratinocytes in the upper layers.

Q. Basal cell carcinoma and actinic keratosis also arise from the basal layer?
- Basal cells are the one that can be damaged by UVR leading to neoplastic proliferation.

Q. What does UVR do to the basal cells?
- UV rays damage the DNA of basal keratinocytes causing functional loss of TP53 (a suppressor gene). TP53 mutation with loss of suppressor function leads to neoplastic proliferation of keratinocytes.

Q. If basal cells become neoplastic, then how do you explain different looks of BCC, AK and SCC under microscope?
- In BCC, the neoplastic cells retain the cytologic features of basal cells (small epithelioid cells, dark basophilic cytoplasm, very little keratin in cytoplasm, small dark nuclei).
- On the other hand, the neoplastic cells in actinic keratosis and squamous cell carcinoma show more maturity, larger cell size and abundant amount of keratohyaline granules in the cytoplasm. That’s why in low power, these tumors are more reddish than the basal cell carcinoma.
**Squamous cell carcinoma in situ** (Intraepidermal squamous cell carcinoma, Intraepithelial squamous cell carcinoma, Non-invasive squamous cell carcinoma, Bowen’s disease)

and

**Invasive squamous cell carcinoma**

**SCC in situ**
Entire thickness of the epidermis is occupied by neoplastic squamous cells. There is no invasion of the dermis because the basal lamina is intact and not broken through by the tumor cells.

**Invasive SCC**
Here the neoplastic squamous cells have invaded the underlying dermis. Once the tumor cells break through the basal lamina into the dermis, it becomes an invasive SCC.
• **Squamous cell carcinoma grading:**

• **Three histologic grades**, based on the degree of nuclear atypia and keratinization

• **Well differentiated**: More normal-appearing nuclei with abundant cytoplasm and keratin pearls.

• **Moderately differentiated**: Features in between well-differentiated and poorly differentiated tumors.

• **Poorly differentiated**: High degree of nuclear atypia, increased mitoses, higher nuclear-cytoplasmic ratio, minimal keratinization.

• **Variations of squamous cell carcinoma**

• **Most of the SCC will be easily diagnosable typical keratinizing squamous cell carcinoma, SCC in-situ or invasive SCC.**

• But in Pathology, there is no lack in variations. I will mention just a few.

• 1. Well differentiated squamous cell carcinoma, keratoacanthoma type

• 2. Verrucous carcinoma

• 3. Acantholytic squamous cell carcinoma

• 3. Spindle cell squamous cell carcinoma

• 4. Clear cell squamous cell carcinoma
Squamous cell carcinoma in situ. F 74, left temple

Compact hyperkeratosis, full-thickness dysplastic keratinocytes, intact basal lamina, no invasion of dermis by the neoplastic keratinocytes.
Squamous cell carcinoma in situ. M 76, left neck

- Compact hyperkeratosis
- Full-thickness dysplastic keratinocytes
- Intact basal lamina
- No invasion of dermis by the neoplastic keratinocytes.
Squamous cell carcinoma in situ. M 76, forehead

Compact hyperkeratosis

Full-thickness dysplastic keratinocytes

Intact basal lamina

No invasion of dermis by the neoplastic keratinocytes.
Invasive squamous cell carcinoma. M 97, left ear lesion

Pleomorphic neoplastic keratinocyte nodules invading the dermis. Tumor cells form round nodules with concentric, laminated layers of keratin called keratin pearls.
Invasive squamous cell carcinoma. M 72, dorsum, left hand

Pleomorph neoplastic keratinocyte nodules invading the dermis. Tumor cells form round nodules with concentric, laminated layers of keratin called keratin pearls.
**Invasive squamous cell carcinoma.**  F 81, left cheek

Pleomorphic neoplastic keratinocyte nodules invading the dermis. Tumor cells form round nodules with concentric, laminated layers of keratin called keratin pearls.
Well differentiated squamous cell carcinoma, keratoacanthoma type. F 81, forehead

Keratoacanthomas (KA) is composed of well-differentiated keratinocytes showing a mild degree of pleomorphism and forming masses of keratin that constitute the central cup-shaped core. The neoplastic keratinocytes are pale and clear due to large amount of cytoplasmic glycogen. Neutrophilic infiltration of the tumor cells are commonly seen.
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Keratoacanthoma is a well differentiated keratinocytic tumor characterized by rapid growth over a few weeks to months, followed by spontaneous resolution over 6 months in most cases.

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Keratoacanthoma Should Be Reported As 'Well Differentiated Squamous Cell Carcinoma, Keratoacanthoma Type': A Dermatopathologist's View

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Keratoacanthomas are skin neoplasms of older adults typically occurring on the sun-exposed hair-bearing locations. The patient usually presents with a history of a rapidly growing tumor over 1-2 months. Clinical examination shows a dome-shaped skin nodule with a central crater filled with keratinous material. If left alone, many of the lesions will completely regress or involute over several months to a year. However, some of the lesions may be very destructive and may even metastasize like squamous cell carcinoma.

Can the dermatologists be absolutely sure about the diagnosis of keratoacanthoma from the clinical presentation and the physical findings? Will they advise the patient that the lesion will disappear over time? Or will they biopsy the lesion and ask the pathologist to tell them whether it is a keratoacanthoma or squamous cell carcinoma? If diagnosed as keratoacanthoma, will they leave it alone? Or will they like to excise the whole lesion with clear margins as if it were a well differentiated squamous cell carcinoma and advise the patient that the lesion has been eradicated?
Microscopic examination of a keratoacanthoma shows a central cup-shaped keratin-filled crater with proliferating squamous epithelial cells extending into the dermis. Normal epidermis extends over the sides of the crater. In the dermal islands of the epidermal cells, the keratinocytes are large with pale glassy eosinophilic cytoplasm with bland nuclei. The base of the lesion may show mitoses and considerable nuclear pleomorphism, especially in the early lesions. Neutrophilic infiltration or microabscesses within the large keratinocytes may be seen.

Can the pathologists definitely say that the biopsy represents a self-regressing keratoacanthoma? Can it be a well differentiated squamous cell carcinoma? Can they assure the clinicians that the lesion may be safely monitored without any chance of it behaving like a carcinoma? Based on the histologic appearance, can the pathologists forecast its future course? Are the pathologists calling the lesion keratoacanthoma and also recommending complete excision like that of a squamous cell carcinoma?

During my last 30 years of dermatopathology practice, diagnosing keratoacanthoma has remained problematic. I have reported the so-called keratoacanthoma by one of many ways:
Keratoacanthoma
Keratoacanthoma with possible squamous cell carcinoma
Keratoacanthoma, squamous cell carcinoma cannot be excluded
Keratoacanthoma/squamous cell carcinoma
Keratoacanthoma/possible regressing squamous cell carcinoma
Keratoacanthoma/self-healing squamous cell carcinoma
Keratoacanthomatous squamous cell carcinoma
Well differentiated squamous cell carcinoma with features of keratoacanthoma
Well differentiated squamous cell carcinoma, keratoacanthoma variant
Well differentiated squamous cell carcinoma/ keratoacanthoma
Well differentiated squamous cell carcinoma, keratoacanthoma type.
This shows that the histologic diagnosis of keratoacanthoma is rarely ever definitive for a pathologist. From all the discussions that I had with my clinical colleagues over the years, I have learned that they are rarely ever sure about the self-regressing keratoacanthoma. Most of them would like the pathologist to tell them if the lesion could be a squamous cell carcinoma. For an apprehensive patient with a fast-growing tumor, they would prefer treating it immediately instead of waiting to see if it regresses! Currently, dermatologists would rather treat it like a well differentiated squamous cell carcinoma with complete resection for many clinical reasons including: avoiding potential cases of keratoacanthoma with metastasis (1), avoiding the potential destructive local effects of some keratoacanthomas, and sparing the patient of a potentially disfiguring scar after regression of the lesion. I find no good reason to separate keratoacanthoma from well differentiated squamous cell carcinoma. I am now reporting crateriform squamous epithelial lesions (that I used to report as keratoacanthoma) as ‘well differentiated squamous cell carcinoma, keratoacanthoma type’. They may then be treated as a well differentiated squamous cell carcinoma with a superficial complete resection, and the patient is relieved of a fast-growing lesion. A small scar is definitely acceptable!

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References
Verrucous carcinoma

M 58, tumor in the left leg amputation stump

5.0X5.0 cm raised, exophytic, and fungating mass with central ulceration over the distal aspect of the stump
Papillomatous epidermal tumor with hyperkeratosis and pushing type of dermal invasion by well-differentiated keratinocytes.
About 60,000 leg amputations are performed each year in the United States. These patients are usually fitted with leg prosthesis. The distal aspect of the stump has the scar from surgical closure. Whereas malignant tumor, commonly a squamous cell carcinoma is known to occur in scarred tissue from burn, chronic ulcers, wounds, sinus and fistulous tracts, the occurrence of cancer in amputated leg stump is very rare.

Review of the English literature reveals only five additional cases occurring in men with an average age of 65 years and after a mean lag period of 40 years between the amputation and development of a low-grade squamous cell carcinoma. Malignancy occurring in leg amputation stump remains a rare event as evidenced by only six such reported cases (including the present case) in the English literature since 1965.

All the patients were male, aged 56 to 75 years with a mean age of 63 years. Amputation was done mostly for trauma. In two cases burn from dynamite and mine explosion was an additional factor. The time between the amputation and the development of malignancy at the stump ranged from 27 to 52 years with a mean lag period of 40 years. All patients developed low-grade squamous cell carcinoma, of which two patients showed a verrucous type of squamous cell carcinoma.

Ref:
Acantholytic squamous cell carcinoma. M 75, face

Histologically, the tumor is composed of strands and islands of dysplastic 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 focal. Tumor islands may show tubular and alveolar formations and clefts due to loss of cohesion, which are referred to as pseudoglandular pattern.

Acantholytic squamous cell carcinoma is also called adenoid or pseudoglandular SCC.
Spindle cell squamous cell carcinoma (Spindle cell carcinoma), M 78, left ear
In the spindle cell variant, atypical spindle cells emanate from the epidermis and form whorls intermingling with strands of collagen.

Within the dermis, the cells form intertwining fascicles and bundles. Individual tumor cells have indistinct borders and contain eosinophilic cytoplasm.

Nuclei are hyperchromatic or vesicular and elongated. Nuclei may be pleomorphic and contain multiple nucleoli.

Mitotic activity is brisk and atypical forms may be seen.

With cellular pleomorphism and tumor giant cell formation, the tumors can bear a close resemblance to atypical fibroxanthoma.

Connection of malignant tumor cells to the epidermis or foci of more typical squamous differentiation favor spindle cell carcinoma.

Cytokeratin stains are usually helpful. In addition, cells can stain positively with mesenchymal markers such as vimentin and smooth muscle actin.
Clear cell squamous cell carcinoma (Squamous cell carcinoma, clear cell type).
M 56, left temple
Immunostain: CK AE 1/3 positive
Clear cell squamous cell carcinoma

Site: Sun-exposed areas like head and neck.

Elderly male.
Clear cells may be focal in a typical SCC or may form the bulk of the tumor.

This variant of SCC shows extensive hydropic changes. The hydropic degeneration of neoplastic cells and the accumulation of intracellular fluid and not the accumulation of glycogen, lipid, or mucin, results in its clear cell appearance.

Differential diagnosis:
Clear cell BCC, trichilemmal carcinoma, sebaceous carcinoma, clear cell eccrine carcinoma, clear cell melanoma, clear cell AFX, metastatic clear cell carcinoma from kidney
Prognosis of SCC of the skin

Cutaneous SCC is not often fatal but it can cause significant morbidity.

Recurrence rate is less than 10% after proper treatment.

There is a low risk of metastasis from a SCC of the skin.

Overall 5-yr survival rate is > 90% after adequate treatment.

• Factors in high-risk SCC
  Tumor location (lips, ears, anogenital region, arising in scar or chronic wound)
• Tumor size (greater than 2 cm)
• Invasion to subcutaneous tissue
• Poorly differentiated neoplastic cells
• Recurrent tumor
• Perineural involvement

• SCC of the skin in patients on immunotherapy or suffering from lymphoproliferative disorders may be more aggressive.