KERATOACANTHOMA
A Tumor *Sui Generis* or a Type of Squamous Cell Carcinoma

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The understanding of the nature keratoacanthoma has been controversial since its original description. Although perceived commonly as a benign neoplasm, papers describing aggressive behavior in keratoacanthomas have been published periodically.[1, 2]

Hutchinson is credited with the first description in 1888-9 and Freudenthal, with the term keratoacanthoma, in the late 1930’s.

- Crateriform ulcer of the face (Hutchinson 1889)
- Verrucom (Gougerot 1929)
- Kyste sébacé atypique (Dupont 1930)
- Molluscum sebaceum (MacCormack & Scarff)
- Tumorlike keratoses (Poth 1939)
- Idiopathic cutaneous pseudoepitheliomatous hyperplasia (Grinspan & Abulafia)
- Keratoacanthosis (Helwig 1955)
- Molluscum pseudocarcinomatous (Linell & Mansson 1958)
- Inverted wart (Brothers et al. 1960)
- Pseudocarcinoma (Peterkin 1962)

The concept of keratoacanthoma evolved through the years, perceived usually as a benign regressing neoplasm. The sporadic report of metastasizing “keratoacanthomas” rang as an alarm, but most papers included a single case. In fact, up to 1994 there were only 12 cases properly recorded.[2]
The concept of keratoacanthoma evolved not only in the general literature but also in individual authors.

To wit:

Keratoacanthoma is a singular neoplasm. No other cutaneous new growth evolves so rapidly and yet resolves so predictably and completely.

-Ackerman 1976 [3]

The prototype of a cutaneous pseudomalignant neoplasm is a keratoacanthoma. Ordinarily, this essentially benign neoplasm springs from the epithelium of the hair follicles, often displays considerable cytological atypia in its development, and extends deep into the dermis or into the subcutaneous fat before eventually resolving spontaneously.

-Ackerman, 1976 [4]

We now add three more examples of what seem to us to be metastasizing keratoacanthomas. Observations of these neoplasms has led us to conclude that keratoacanthoma is, in actuality, an expression of squamous-cell carcinoma….We now regard solitary keratoacanthoma as a squamous-cell carcinoma, a type that has a distinctive appearance and in the vast majority of instances undergoes resolution without therapy.

-Hodak, Jones, & Ackerman, 1993 [2]

This 1993 publication has been extremely influential and a turning point in changing the perception of keratoacanthoma as a self-limited benign neoplasm and considering it a potentially aggressive tumor, namely squamous cell carcinoma.
This presentation will address the following issues:

1. Is keratoacanthoma a benign self-limited neoplasm different from squamous cell carcinoma?
2. Is keratoacanthoma a variant of squamous cell carcinoma?
3. Can the self limited KA become a progressive SCC somewhere in its clinical course?
4. Can KA and SCC be differentiated histologically?

Keratoacanthoma denotes a spectrum of benign, cup-shaped tumors of keratinocytes that develop rapidly and undergo spontaneous regression. It is morphologically similar to well differentiated squamous carcinoma and, in fact, some authors believe it is an abortive carcinoma.[5] There are differing opinions on the nature of keratoacanthomas; some authors reject the diagnosis altogether [2], while others embrace the diagnosis as one that can be made, but must be used with caution. Clinically, keratoacanthomas are lesions that usually develop on the sun-exposed skin of the elderly [6]; these are known also as actinic keratoacanthomas. Less common variants include those that occur on sun-protected skin, in immunosuppressed individuals [7], giant forms (keratoacanthoma marginatum centrifugum), multiple and syndromic forms,[8] and subungual keratoacanthoma.[9-11]

CLINICOPATOLOGICAL VARIANTS

- Actinic
- Non actinic
- Follicular
- Subungual
- Giant
- Centrifugum marginatum
- Multiple (Ferguson-Smith)
- Eruptive (Grzybowski)
Keratoacanthomas have a rapid clinical evolution and often resolve in months. Typically many keratoacanthomas have been present only for a few weeks when biopsied. Keratoacanthomas can be treated with excision or just close clinical follow-up after establishment of the histologic diagnosis.

Histologically, keratoacanthomas have different features depending upon the evolutionary stage of the lesion when biopsied. Like most tumors, such as mycosis fungoides, melanoma, and Kaposi sarcoma, there are three recognizable stages:

- Early growing phase
- Fully developed phase
- Senescent phase

Obviously, unlike those other neoplasms, the third phase of keratoacanthomas is regression and not progression to nodular stages.

The early keratoacanthoma is a small, mostly solid tumor with scant keratinization and inflammation. There is variable cellular pleomorphism.
Most keratoacanthomas are biopsied in the developed phase. At this stage there are symmetric, crateriform, exophytic lesions containing a central keratin plug and deep bulbous lobules of squamous cells containing abundant eosinophilic, translucent cytoplasm which is typically termed “glassy”. There is a “lip” of normal epidermis at the periphery that extends partially over the central keratinous crater.
Cytologically, the keratinocytes vary from monomorphous and uniform to pleomorphic and with numerous mitotic figures, but none of these features will help determine the diagnosis with certainty. There is a gradient of cellular pleomorphism with most of the pleomorphic keratinocytes at the periphery of the deep lobules. This contrasts with squamous cell carcinomas in which the pleomorphism is usually random. Yet, architectural features are more helpful than cytological features in establishing the diagnosis. [12]

Apoptotic keratinocytes are usually present in the lobules. Fully keratinized cells are seen in microcavities; when this occurs, it is usually parakeratotic and is often associated with neutrophilic microabscesses as well as elastic and collagen fibers.[13]
The inflammatory infiltrate around the periphery of the lesion is lichenoid in nature with lymphocytes and eosinophils; plasma cells are found only rarely.

A band of fibrosis beneath the lesion can be seen at this stage. This represents an early sign of regression and it is a useful diagnostic finding.

The penetration and presence of intraepithelial elastic fibers, elastotic material and collagen is highly characteristic of keratoacanthomas. This finding can also be seen in squamous cell carcinomas, but usually in lesser degree. The trapping of elastic tissue is seen in all the growth phases of keratoacanthoma. It is more evident at the peripheral areas of the tumor lobules.
Perineural involvement may be observed, sometimes extensively, along the deep portion of the tumor. Its presence is not particularly helpful in differentiating keratoacanthoma from squamous cell carcinoma. [14-15]

Vascular invasion may occur rarely, but is not necessarily associated with adverse outcome [16] although it is certainly a worrisome feature.

In the regressive or senescent phase, keratoacanthomas hollow out, filling the crater with keratin. The solid lobules of keratinocytes largely disappear, being replaced by a mature keratinous cyst-like epithelium. The lesion becomes shallow, losing the crater-like qualities. At this time the lesion closely resembles an inflamed seborrheic keratosis. Dense, confluent fibrosis is present, and it replaces the reticular dermis.
In unusual cases, lesions in the histologic spectrum typical of keratoacanthoma will pursue an aggressive clinical course, suggesting that the initial lesion was diagnosed incorrectly or that the differentiation from some squamous carcinomas is not always possible by conventional microscopy and clinicopathologic correlation.[2]
DIFFERENTIAL DIAGNOSIS BETWEEN KERATOACANTHOMA AND SQUAMOUS CELL CARCINOMA

<table>
<thead>
<tr>
<th>CRITERION</th>
<th>KERATOACANTHOMA</th>
<th>SQUAMOUS CARCINOMA</th>
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<tbody>
<tr>
<td>GROWTH RATE</td>
<td>Rapid growth (weeks to months)</td>
<td>Slow growth (months to years)</td>
</tr>
<tr>
<td>SYMMETRY</td>
<td>Symmetrical dome with overhanging “lips”</td>
<td>Asymmetric and slightly raised or ulcerated</td>
</tr>
<tr>
<td>KERATIN PLUG</td>
<td>Central, common</td>
<td>Rare</td>
</tr>
<tr>
<td>TRANSITION ZONE</td>
<td>Abrupt transition between tumor and epidermis</td>
<td>Gradual transition of normal epidermis to squamous cell pleomorphism to tumor</td>
</tr>
<tr>
<td>CYTOLOGIC PLEOMORPHISM</td>
<td>Variable, some are very pleomorphic, vertical “gradient”</td>
<td>More common. diffuse</td>
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<tr>
<td>CYTOPLASM</td>
<td>Abundant, often “glassy” or eosinophilic</td>
<td>Irregular, abundant or scant</td>
</tr>
<tr>
<td>ACANTHOLYSIS</td>
<td>Not seen</td>
<td>Frequent</td>
</tr>
<tr>
<td>INTRAEPITHELIAL NEUTROPHILIC ABScesses</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>KERATINIZATION PATTERNS</td>
<td>Orthokeratotic with frequent granular layer</td>
<td>Usually parakeratotic, acantholysis</td>
</tr>
<tr>
<td>INTRAEPITHELIAL ELASTIC TISSUE</td>
<td>Common in peripheral tumor nests</td>
<td>Uncommon in peripheral tumor nests</td>
</tr>
<tr>
<td>ELASTOPHAGOCYTOSIS</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>INFLAMMATORY INFILTRATE</td>
<td>Common, dense and lichenoid</td>
<td>Variable</td>
</tr>
<tr>
<td>EOSINOPHILS</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>PLASMA CELLS</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>PERINEURAL INVASION</td>
<td>Rare, but present in deeper tumors</td>
<td>Rare</td>
</tr>
<tr>
<td>SUBCUTANEOUS INVOLVEMENT</td>
<td>Not uncommon in large tumors</td>
<td>Not uncommon in large tumors</td>
</tr>
<tr>
<td>FIBROSIS</td>
<td>Dense, band-like, located deep to the lesion</td>
<td>When present, surrounds tumor nests</td>
</tr>
<tr>
<td>RESOLUTION</td>
<td>Spontaneous</td>
<td>None, without therapeutic intervention</td>
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There have been attempts to find a way to differentiate keratoacanthoma from squamous cell carcinoma by using modern techniques; these have not met with great success.[17] For instance, there have been attempts to show that the expression of p53 might differentiate the two conditions.[5,18,19] However, even controls, such as pseudocarcinomatous hyperplasia, express p53, and it appears that the expression of p53 protein, mutant or wild type, is an indicator of immaturity and proliferative capacity of the cell rather than one type of neoplasia or malignancy.[19] The expression of bcl-2, a proto-oncogene recognized to be involved in protecting cells from undergoing apoptosis, is diminished in keratoacanthomas when contrasted with squamous carcinomas,
suggesting that keratoacanthoma, for unknown reasons, is programmed to involute, [20] but one would hardly base a diagnosis on this parameter alone. The proliferation antigen, Ki-67, is likewise expressed in both types of lesions and will not serve to differentiate them.[2,18] Other methods, such as immunohistochemical demonstration of desmosomal glycoproteins,[21] may be a useful adjunct, but are not definitive.

I continue to believe that keratoacanthoma is a useful diagnosis and, if made in a proper clinical context, is a service to the patient and to the clinician treating the patient. The distinction between keratoacanthoma and squamous cell carcinoma can be made with confidence most of the time, particularly if the pathologist is provided with an adequate biopsy.

Issues that remain to be solved are whether keratoacanthoma is a sui generis self-limited, regressing epithelial neoplasm or a variant of squamous cell carcinoma. If a squamous cell carcinoma, does it have the same biological potential, since most cutaneous squamous cell carcinomas follow a usual non metastasizing clinical course.

Is the diagnosis of squamous cell carcinoma, keratoacanthoma type a bona fide diagnosis, or just a euphemism to avoid making a committed diagnosis of a benign neoplasm?

In the current legal climate, it is understandable why one might want to abandon the concept of keratoacanthoma, but I don’t believe that serves our patients well.
REFERENCES


