DIAGNOSTIC APPROACH TO KERATOACANTHOMA: DIFFERENTIATING WITH SQUAMOUS CELL CARCINOMA

Firda Fakhrena, A.A Ayu Adisti Nina Yuniandari, Rafdi Ahmed, Diana Wijayati
Departement of Dermatology and Venereology, Cibabat Hospital Cimahi West Java, Indonesia
Email: fakhrena12@gmail.com, adisti.nina@gmail.com, fakhrimskartanegara@gmail.com, agungayunina@gmail.com

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ABSTRACT
Keratoacanthoma (KA) is a cutaneous neoplasms from the pilosebaceous unit, characterized as a rapidly growing tumor and usually show spontaneous regression. A major difficulty in dealing with these neoplasms is to differentiating them from squamous cell carcinoma, clinically and histologically. However, the change for regression has led keratoacanthoma as benign tumors with different pathophysiological mechanism from cutaneous squamous cell carcinoma (cSCC). The similarities between keratoacanthoma and cSCC, especially the well-differentiated variant cSCC, has led to the general recommendation for surgical excision of keratoacanthoma to make sure that a potentially malignant cSCC is not left untreated. Differentiating KA with cSCC would change management strategies to the less invasive treatment modalities, prevent surgical morbidity, and reduce healthcare costs. Methods: We searched for relevant journal articles in PubMed with a systematic search using PICO, with the keyword “Keratoacanthoma” or “Squamous cell carcinoma” and “Diagnostic” or “History, physical examination, histology”. We got 825 publications and we filtered by the last five years and we generated 12 publications from 2017-2022 after we checked from the title and abstract for relevancy. Conclusion: The review revealed that keratoacanthoma can be distinguished from squamous cell carcinoma from the biological differences of spontaneous regression, very rapid growth and the absence of malignant features. It can also be distinguished by the histological and immunohistochemistry examination such as the presence of epithelial lips, neutrophilic microabscesses within the atypical epithelium, firm boundaries between tumor and stroma, ulceration, many mitotic cells and pleomorphic or anaplastic. The study also show that CD1a and Hsp60 can help distinguish between KA and SCC.

Introduction
Keratoacanthoma (KA) is an epithelial tumor from pilosebaceous unit characterized with rapidly growing and spontaneous regression (Bilgen et al., 2020). KA is also defined as a benign neoplasm which arises from hair follicle. KA usually occur as a single dome shaped with a central crater filled with keratin (Connolly et al., 2008). This tumor has three growth phases including proliferation, maturation, and regression which occur for 4-6 months. KA size reaches...
approximately 10-25 mm within 6 to 8 weeks (Park et al., 2015). When the size of KA is more than 2 cm, it is called giant KA. Predilection areas of KA are usually in sun-exposed skin (Gleich et al., 2016). Giant KA is a rare case and to our knowledge, there is no collective incidence reported in Indonesia. Peak incidence of KA is at 50-69 years of age (Garcia-Zuazaga et al., 2009). The incidence was found more in men than women with ratio of 2:1. Skin type of Fitzpatrick I-II classification often becomes one of the risk factors (Wolff et al., 2008). Sun-exposed regions such as face, head, neck, and dorsal extremity are the predilection of this disease. Lesion is usually appear single rather than multiple (Nicolaídu & Katsambas, 2014). Other causes of KA are exposure to UV light radiation, carcinogenic chemical material, genetic predisposition, human papillomavirus (HPV) infection, trauma, or history of surgery at the lesion site (Patrick M. Zito & Richard Scharf, 2022). Keratoacanthoma has three phases of growing include proliferation, maturation, and regression which occur for 4-6 months (Gibson-Corley et al., 2014). Proliferation phase occurs rapidly within 6 to 8 weeks until reaches 10-25 mm in size (Park et al., 2015), and becomes stable in the maturation phase within months (generally 6 months) and finally spontaneous regression to atrophic scar or hypopigmentation lesion. Typical single KA can grow to 2 cm in size, and appear as a red nodule with central keratin plug. After this phase, lesion becomes smaller until regress completely (Goldberg et al., 2004). When the size of KA is more than 2 cm, it is called giant KA. Giant KA often be found in eyelids and nose (Gleich et al., 2016); (Garcia-Zuazaga et al., 2009).

Diagnosis of KA is often similar clinically and histologically to squamous cell carcinoma (Patrick M. Zito & Richard Scharf, 2022). Yet, this still becomes controversy. A major difficulty in dealing with these neoplasms is to differentiating them from squamous cell carcinoma, clinically and histologically (Mandrell & Santa Cruz, 2009). However, the change for regression has led keratoacanthoma as benign tumors with different pathophysiological mechanism from cutaneous squamous cell carcinoma (cSCC) (Bălășescu et al., 2022). The similarities between keratoacanthoma and cSCC, especially the well-differentiated variant cSCC, has led to the general recommendation for surgical excision of keratoacanthoma to make sure that a potentially malignant cSCC is not left untreated (Tisack et al., 2021). Differentiating KA with cSCC would change management strategies to the less invasive treatment modalities, prevent surgical morbidity, and reduce healthcare costs (Kerschmann et al., 1994). This article will summarize the diagnostic approach of keratoacanthoma, and differentiating them from the squamous cell carcinoma.

Methods

We searched for relevant journal articles in PubMed with a systematic search using PICO, with the keyword “Keratoacanthoma” or “Squamous cell carcinoma” and “Diagnostic” or “History, physical examination, histology”. We got 825 publications and we filtered by the last five years. Only 12 publications from 2017-2022 were chosen after we checked from the title and abstract for relevancy to our study.

Result and Discussion

A. Clinical Behavior of Keratoacanthoma

Keratoacanthoma (KA) is an epithelial tumor from pilosebaceous unit characterized with rapidly growing and spontaneous regression (Bansal et al., 2012). KA is also defined as a benign neoplasm which arises from hair follicle. KA usually occur as a single dome shaped with a central crater filled with keratin (Cohn et al., 2017). This tumor has three growth phases including proliferation,
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maturation, and regression which occur for 4-6 months. KA size reaches approximately 10-25 mm within 6 to 8 weeks (Park et al., 2015). When the size of KA is more than 2 cm, it is called giant KA. Predilection areas of KA are usually in sun-exposed skin (Gleich et al., 2016). Giant KA is a rare case and to our knowledge, there is no collective incidence reported in Indonesia.

Peak incidence of KA is at 50-69 years of age (Garcia-Zuazaga et al., 2009). The incidence was found more in men than women with a ratio of 2:1. Skin type of Fitzpatrick I-II classification often becomes one of the risk factors (Wolff et al., 2008). Sun-exposed regions such as face, head, neck, and dorsal extremity are the predilection of this disease. Lesion is usually appear single rather than multiple. Other causes of KA are exposure to UV light radiation, carcinogenic chemical material, genetic predisposition, human papillomavirus (HPV) infection, trauma, or history of surgery at the lesion site (Patrick M. Zito & Richard Scharf, 2022). Keratoacanthoma has three phases of growing include proliferation, maturation, and regression which occur for 4-6 months. Proliferation phase occurs rapidly within 6 to 8 weeks until reaches 10-25 mm in size (Park et al., 2015), and becomes stable in the maturation phase within months (generally 6 months) and finally spontaneous regression to atrophic scar or hypopigmentation lesion. Typical single KA can grow to 2 cm in size, and appear as a red nodule with central keratin plug. After this phase, lesion becomes smaller until regresses completely. When the size of KA is more than 2 cm, it is called giant KA. Giant KA often be found in eyelids and nose (Gleich et al., 2016); (Garcia-Zuazaga et al., 2009).

Table 1. Variant of Keratoacanthoma and Syndrome

<table>
<thead>
<tr>
<th>Type of KA</th>
<th>Clinical Features</th>
<th>Genetic Defect</th>
</tr>
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<tbody>
<tr>
<td>Solitary KA</td>
<td>Most common, sporadic, 5-15 mm solitary lesions</td>
<td>Mutiple (Wnt and TP63 upregulation)</td>
</tr>
<tr>
<td>KA Centrifugum Marginatum</td>
<td>Solitary or multiple annular plaques progressively expanding peripherally with elevated, rolled margins and central resolution rapidly reaching 3 cm in diameter, but may be as large as 30 cm</td>
<td>HPV 6 and 11</td>
</tr>
<tr>
<td>Giant KA</td>
<td>Greater than 2-3 cm, can be &gt;20 cm in diameter associated with slower, but prolonged, growth and frequently involving the nose and eyelids</td>
<td>HPV 6 and 11</td>
</tr>
<tr>
<td>Generalized Eruptive KA of Grzybowski</td>
<td>Thousands of papules esembling milia or xanthomas with frequent mucous membrane involvement and severe pruritus most frequently affecting patients in their 50s – 70s; resolve slowly over months with scarring and ectropion; associated with visceral malignancies</td>
<td>HPV 16 and 39</td>
</tr>
<tr>
<td>Multiple self-healing squamous epithelioma (Ferguson)</td>
<td>Multiple spontaneously regressing Kas in sun-exposed sites beginning in the third decade of life; regress over weeks to months; overlapping features of Grzybowski and of Witten and Zak</td>
<td>Autosomal dominantly inherited loss-of-function mutations in TGFBR1</td>
</tr>
</tbody>
</table>
B. Physical Examination of Keratoacanthoma

Keratoacanthoma is usually solitary rather than multiple. It starts from papule and change to the dome-shaped papule, well demarcated, and then becomes an umbilicated nodule with the hyperkeratotic plug in the center within 4 to 6 months and can heal with or without a scar.

C. Histology of Keratoacanthoma

Histologically, keratoacanthoma show an epithelial proliferation with a cup-shaped, show a prominent acanthosis consist of glassy keratinocytes. A central keratin-filled crater is usually seen with the epidermis extends medially over the crater shape like a lip. In the underlying dermis, the epithelial proliferation is invaginated which often show a solar elastosis. Neutrophilic microabscesses within the atypical epithelium is a characteristic finding of keratoacanthomas. In the surrounding dermis, a lymphocyte-rich inflammatory infiltrate is frequently observed. Dyskeratotic keratinocytes often presence and accompanied by fibrosis of the surrounding stroma and forms a scar.

D. Differentiating Keratoacanthoma with cSCC

Compared to squamous cell carcinoma, keratoacanthoma involuted spontaneously within several months and one year. Keratoacanthoma growth rapidly than squamous cell carcinoma, however its possibility of metastasize is as high as 5%. The histopathologic of keratoacanthoma are phase dependent.

1. Early lesions consist of an exoendophytic proliferation of pale squamous cells in lobules, and infundibular distortion, extend to reticular dermis

2. In later biopsies, the infundibular structures become more cystic and hyperkeratotic, to form a central keratin plug

3. Regression lesions are characterized by a well formed crater of keratin with a thin of surrounding squamous epithelium, fewer squamous lobules and progressive development of underlying dermal fibrosis.

Well developed keratoacanthoma are symmetric with most peripheral tumor islands infiltrates beyond the central mass. The main histopathologic features which are to exclude a keratoacanthoma and confirm diagnosis of cSCC are the presence of asymmetry, extension beyond the sweat glands, sign of infiltration and desmoplasia.
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Explanation of the picture one:

1. Proliferative (early) phase:
   A, clinical presentation: papulonodular lesion that gradually develops central hyperkeratosis and punctum, (consistent with early keratinous core). B and C, histopathologic features: invaginations of acanthotic squamous epithelium with infundibular differentiation

2. Stabilized (well-developed) phase:
   D, clinical presentation: nodular lesion with central keratotic core; E and F, histopathologic features: exo-endophytic squamous proliferation with crateriform architecture and central keratotic core, composed of large keratinocytes with abundant glassy eosinophilic cytoplasm and small ovoid nuclei, recapitulating isthmic differentiation and scattered neutrophils

3. Regressive (late) phase:
   G, clinical presentation: progressively flattening hyperkeratotic lesion with erythematous rim and fibrosis that gradually scars completely; H and I, histopathologic features: perilesional lymphohistiocytic infiltrate and increasing fibrosis surrounding irregular invaginations of squamous epithelium with atrophy and infundibular differentiation with loss of keratinous core.

In other literature, the histopathological differences between KA and SCC are based on five significant criteria for KA: 1. Epithelial lips 2. Firm boundaries between tumor and stroma 3. Ulceration 4. Many mitotic cells, 5. Pleomorphic or anaplastic.

<table>
<thead>
<tr>
<th>Table 2. Differences of KA and SCC; biological and histopathological</th>
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<tbody>
<tr>
<td><strong>KA</strong></td>
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<tr>
<td>Biological differences</td>
</tr>
<tr>
<td>Rapid growth till 1-2 cm</td>
</tr>
<tr>
<td>Involution</td>
</tr>
<tr>
<td>Exoendophytic</td>
</tr>
<tr>
<td>Histopathologic differences</td>
</tr>
<tr>
<td>Epithelial lips</td>
</tr>
<tr>
<td>-</td>
</tr>
<tr>
<td>Intraepithelial abscesses in the lesion</td>
</tr>
<tr>
<td>Rare ulceration</td>
</tr>
</tbody>
</table>
**Distinct edge between tumor and stroma**

<table>
<thead>
<tr>
<th></th>
<th>Indistinct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraepithelial abscesses with acantholytic cells</td>
<td>No association between eosinophils and acantholytic cells</td>
</tr>
<tr>
<td>Flask shaped</td>
<td>-</td>
</tr>
<tr>
<td>Epitelial colarette</td>
<td>Rarely observed</td>
</tr>
<tr>
<td>Symmetric</td>
<td>Asymmetric</td>
</tr>
<tr>
<td>-</td>
<td>Melanocyte present</td>
</tr>
<tr>
<td>Absence of stromal desmoplasia</td>
<td>Present</td>
</tr>
</tbody>
</table>

KA metastasis yet still debatable. Keratoacanthoma of the head and neck is potentially aggressive for perineural invasion and metastasis. KA can invade via mimic muscles, cranial nerves, or cavernous sinuses, have a high potential for recurrence, and metastasize to the parotid and regional lymph nodes (Paolino et al., 2017). Nevertheless, other literatures showed that KA metastasis is a false diagnosis, which is actually squamous cell carcinoma. In fact, 10% of tumors diagnosed with KA are malignant squamous cell carcinoma (scCC) (Alfieri et al., 2019). This scenario can be challenge in some ways. First, scCC can probably arise within keratoacanthoma, and this component makes like KA is metastasis. Second, keratoacanthoma that have metastasized may have truly been scCC with the difference follicular pattern. Third, visceral carcinomas that can metastasize to the skin have the capability to disguise as keratoacanthoma (Soddu et al., 2013).

There is a significant prognostic difference between perineural invasion in keratoacanthoma and scCC. Keratoacanthoma has no metastasis and direct death to the presence of perineural invasion in keratoacanthoma. While perineural invasion is a poor prognostic factor in scCC when involve the nerve in subcutan > 0,1 mm in caliber. The literature explain that on a larger study of 3.465 keratoacanthoma, incidence of perineural invasion is 0,2% while scCC range from 2%-14%.

### E. Immunohistochemistry in Keratoacanthoma vs squamous cell carcinoma

Immunohistochemistry is an extremely valuable to standart morphology diagnostic pathology. PCNA/MIB1-labeled proliferating cells are found in keratoacanthoma, especially in the periphery of the squamous nests in keratoacanthoma, in contrast to a more diffuse pattern in SCC. Eighty percent (80%) of keratoacanthoma showed nuclear staining with anti-p53 antibody, distributed along the outermost layers of the aggregates of neoplastic cells. While SCC (60% of SCC) were p53 positive. Regressing keratoacanthoma (8%) also showed p53 positivity. At last finding is used to differentiate regressing KA from normal and reactive epidermis. High staining of p53 favors the diagnosis of subungual SCC rather than subungual keratoacanthoma. Subungual keratoacanthoma do not express strongly of Ki67, whereas subungual SCC do. It is conclude that p53 and Ki67 can help distinguish between a subungual SCC and subungual keratoacanthoma.

The study of CD1a and Hsp60 also show that the level of both are significantly lower for keratoacanthoma than in SCC. It can support the hypothesis that if
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Keratoacanthoma can evolve towards SCC because there is a failure of the local modulation of the anti tumor immune response and the study also show that CD1a and Hsp60 can help distinguish between KA and SCC.

F. Treatment of Keratoacanthoma

Treatment of keratoacanthoma consists of several options, such as excision (Mohs surgery, or standard excision), systemic retinoids, methotrexate intralesional injection, or radiotherapy (Moss et al., 2019); (MacFarlane DF, 2021). In general, excision with electrocautery in combination with curettage is used for superficial lesions that are smaller and located at low-risk lesion sites such as the neck, trunk, and extremities. Moderate or moderate risk is present on the scalp, forehead, around the ears, and malar area. High-risk areas are around the nose, nasolabial folds, eyelids, periorbital area, lip of the chin, and some tumors in the ear. Cure rate of approximately 96% was found with this technique the lesions with size of in 2 cm or less. Larger lesions, which are not superficial, or are in areas of high risk, are not recommended using this technique.7

The reasons we can anticipated for treatment of keratoacanthoma:
1. Minimizing the scars after the regression lesion
2. Avoid local destruction which is follows with the rapid growth of lesion and metastasizes to other organs
3. Unpredictable final size of the lesion
4. Unpredictable course of these tumors that can be aggressive behavior like SCC
5. The initial ambiguities characteristic of the lesion in its growth phase (dilemma to reach a definite diagnosis and the concern of differential diagnose of SCC
6. Tendency KA appear on the face and probably destructs a large area of the tissue because of the ulceration and secondary infection

Conclusion

Keratoacanthoma is an epithelial tumor of the pilosebaseous unit with characteristics of rapid growth and spontaneous regression. Clinically and histopathologically, keratoacanthoma has similarities to squamous cell carcinoma. The similarities between keratoacanthoma and cSCC, especially the well-differentiated variant cSCC, has led to the general recommendation for surgical excision of keratoacanthoma to make sure that a potentially malignant cSCC is not left untreated. Differentiating KA with cSCC would change management strategies to the less invasive treatment modalities, prevent surgical morbidity, and reduce healthcare costs. Keratoacanthoma can be distinguished from squamous cell carcinoma from the biological differences of spontaneous regression, very rapid growth and the absence of malignant features. It can also be distinguished by the histological and immunohistochemistry examination such as the presence of epithelial lips, neutrophilic microabscesses within the atypical epithelium, firm boundaries between tumor and stroma, ulceration, many mitotic cells and pleomorphic or anaplastic. The study also show that CD1a and Hsp60 can help distinguish between KA and SCC.

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