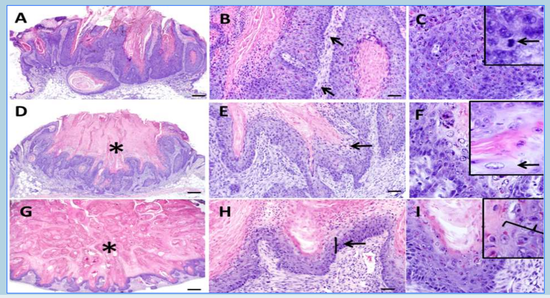
New Aspects In Molecular Biology Of Keratoacanthoma {KA}

Would It Help In Distinguishing Between KA & SCC ?

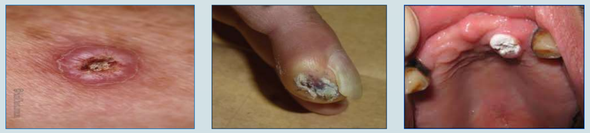
Introduction

- Keratoacanthomas (KA) are common but exceptional benign tumors, often appearing on sun-exposed areas of light skinned people and showing spontaneous resolution.
- Relying on recent results, KA is assumed to be an individual lesion with a unique molecular signature caused by alterations in the TGF-β signaling pathway.
- These recent findings will help to understand the nature of KA and to develop new reliable diagnostic tools, simplifying the discrimination of the histologically similar KA and SCC.



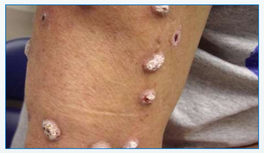
Solitary KA

- **Typical solitary KA:** is rapidly growing up to 2 cm, appearing as a rose nodule with a keratotic centre.
- **Giant KA:** usually grow larger than 2 cm, predominantly appears on eyelids and nose.
- **Subungual KA:** a rare variant which appears under nails. show rarely spontaneous regression and may destroy the terminal phalanx.
- **Mucosal KA: e**xtremely rare variant, which has no tendency to regress and is observed mostly intra-orally. Since intraoral mucous membranes bear no hair follicles it was suggested that these variant of KA may arise from ectopic sebaceous glands.
- **Keratoacanthoma Centrifugum:** is a rare exo-endophytic type, characterized by multi-follicular origin, progressive peripheral expansion (2–40 cm) and atrophic central healing.

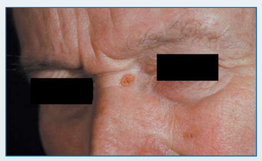


Multiple KA

- **Ferguson Smith type (MSSE):**
  - This autosomal dominant genodermatosis is characterized by sudden appearance and rapid growth, slow regression and periodical recurrence.
  - 11 mono-allelic mutations in transforming growth factor beta receptor 1 (TGF-β1) were identified in this phenotype.

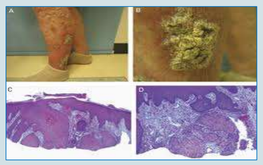


- **KA in Muir-Torre syndrome**:
  - An autosomal dominant genodermatosis which combines visceral malignancy, notably colon cancer with sebaceous neoplasms
  - The syndrome is caused by germline mutations of hMSH2 and hMLH1 genes



- **KA with xeroderma pigmentosum**:
  - Xeroderma pigmentosum is an autosomal recessive disorder caused by defects in genes coding for DNA repair enzymes.
  - Compared to normal cells, cells of XP patients fail to repair UV-induced DNA lesions. This failure of the repair system causes development of melanoma, basal cell carcinoma, SCC and KA.

- **Reactive KA:**
  - **This type of KA** is induced by treatment of melanoma patients with the BRAF kinase inhibitors.
  - The iatrogenic tumor formation usually occurs 8 weeks after inhibitor therapy initiation by paradoxical activation of the ERK MAP kinase pathway



Molecular biology of KA versus SCC

1) TGF- β signalling in KA and SCC:

- The implication of TGF-β signaling in KA formation was demonstrated recently by *Goudie et al*. They ascertain a clear correlation between loss of function mutations in the TGF-βr1 gene and a MSSE phenotype of KA.
- In total, 11 mono-allelic mutations in 18 families have been described, occurring in the cytoplasmic kinase domain or in the extracellular ligand-binding domain.
- The paradoxical role of TGF-β signalling could explain the rapid evolution and involution of KA after ablation of TGF-β mediated signal transduction.
- On the other hand, rather than TGF-βr1 mutations, recently identified NOTCH1/2 receptor mutations are considered as early gatekeeper mutations in SCC development.

2) Par3 signalling in KA formation:

- The Par3 pathway is implicated in KA formation and affects downstream targets of TGFbR1 such as PI3K/Akt and MAPK.
- Specifically, Par3 is involved in apico-basal cell polarity and asymmetric cell division.

3) RAF inhibitors favors KA and SCC development:

- Ninety per cent of all BRAF mutations are V600E changes, causing a higher BRAF activity thereby activating MAPK signalling pathway independently of RAS.
- A side effect of the mutation-specific BRAF V600E drug Vemurafenib in melanoma patients is the appearance of SCC or KA in 15–20% of the patients.
- While melanoma patients treated with Sorafenib also developed SCC or KA lesions in up to 7% of the cases.

Genetics background

- Array comparative genomic hybridization (array CGH) allows the discrimination of KA and SCC in 85% of the cases.
- Recurrent aberrations on chromosome 7, 8 and 10 have been the best predictors for SCC, suggesting a role in prevention of apoptosis or activation of proliferation and infiltration for genes located in these areas.
- In contrast chromosomes 17, 19, 20 and X seemed to be aberrant mainly in KA, indicating crucial genes for KA development.

Conclusion

- The etiology of KA involves many different factors, of which giving rise to a broad spectrum of KA variants.
- Genetic predisposition or spontaneous formation adds another level to the complex classification system of KA.
- Today, it has been concluded that SCC and the benign neoplasm KA are two distinct entities, prototypically evidenced by alterations in the TGF-β pathway in Ferguson Smith Disease, chromosomal aberration differences and pronounced alterations in gene expression.
- Up till now, it is a difficult task to distinguish KA and SCC on histopathological grounds. Consequently, it is essential to find morphological, biological and/or molecular markers which are showing reliable differences between these two lesions to prove that a given KA is not a SCC.
- Recently published data lead us to assume that KA is distinct from SCC and caused by early gatekeeper alterations in the TGF-β pathway.

References

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Presented by

Amal Mostafa Sayed

*B.D.S (Cairo University)

*Master's Candidate At Oral Pathology Department
Faculty Of Dentistry, Cairo University

*Demonstrator At Oral Pathology Department
Faculty Of Dentistry, Egyptian Russian University (ERU)