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Commentary

Caldera, Keratin, Simulation - Keratoacanthoma

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Keratoacanthoma was initially scripted by Hutchison in 1889 and is cogitated as a squamo- proliferative lesion of obscure an etiology which predominantly occurs on sun- exposed skin and infrequently on the mucocutaneous junction. Keratoacanthoma denotes a nomenclature of a self-healing carcinoma, molluscum sebaceum, molluscum pseudocarcinomatosum, self-healing primary squamous cell carcinoma, tumour like keratosis and idiopathic cutaneous pseudoepitheliomatous hyperplasia. It is morphologically challenging to differentiate the centroidal segment of keratoacanthoma from a squamous cell carcinoma.

Keratoacanthoma is designated as a benign skin tumefaction of minimal grade with a potential for expeditious evolution. Lesions are dome shaped with a centralized keratinous plug and range betwixt one centimetre to two centimetre in magnitude.

Keratoacanthoma was contemplated as a malignant skin condition prior to 1917. Lesions were denominated as a verruca or vegetative cyst amidst 1920's whereas betwixt 1936 to 1950 lesions were referred to as molluscum sebaceum.

Keratocanthoma is comprised of subcategories such as solitary keratocanthoma, subungual keratoacanthoma, mucosal keratoacanthoma, giant keratocanthoma, keratoacanthoma centrifugum marginatum, the exceptional, sporadic, pruritic variant generalized eruptive keratoacanthoma of Grzybowski and multiple keratocanthoma associated with Ferguson Smith syndrome [1,2].

Disease characteristics

Keratoacanthoma is engendered within the pilosebaceous unit on account of an anomaly with the follicular infundibulum with ensuing hyperkeratosis. Initial phase of brisk tumour progression with subsequent, varying duration of tumour stability and tumour regression is cogitated.

Evolution of keratoacanthoma is subdivided in stages of proliferation, maturation and involution. Proliferation phase describes a brisk tumour growth extending up to 6 weeks to 8 weeks. Maturation phase is elucidated within several weeks to several months where the lesion develops a keratin filled crater. Involution is the terminal stage where keratoacanthoma demonstrates a regressive, atrophic scar.

Keratoacanthoma appears as singular or multiple lesions. Tumefaction is constituted of well differentiated, keratinised squamous epithelial cells engendered from the pilo-sebaceous unit of hair follicles. The preponderantly self-limiting lesion recapitulates clinical and histological features of squamous cell carcinoma [1,3].

Keratoacanthoma of head and neck represents an estimated 70% instances of the disorder. Implicated aetiological aspects include exposure to sunlight, viral infection with human papilloma virus (HPV), localized and current trauma or surgery, incompetent cellular immunity, actinic factors or ultraviolet radiation, chemical carcinogens (coal and mechanical oil), genetic discordance or mutation of p53 and HRas, chemotherapy, circulating carcinogenic factors and immunologic suppression due to application of hedgehog pathway inhibitors in basal cell carcinoma or BRAF inhibitors in malignant melanoma. Keratoacanthoma can depict a sporotrichoid or lymphatic allocation of lesions.

Keratoacanthoma occurs in individuals from 14 years to 86 years with a mean emergence at 56 years. Approximately 80% instances are diagnosed at above 40 years of age and maximal prevalence of the lesion is betwixt 50 years to 70 years. Solitary keratoacanthoma emerges betwixt 50 years to 69 years of age and is exceptional prior to 20 years of age [2,3].

Gender distribution of the disorder enunciates a male predominance with a M: F ratio of 2::1. Majority of lesions appear in individuals of fair skin, maximally within Fitzpatrick skin types I to III. Tumefaction are predisposed to appear in cosmetically sensitive sites such as nose, hard palate, gingival region, eyelids, cheek, dorsum of extremities and lower lip. Keratocanthoma can appear in regions devoid of sunlight exposure such as mucosal or subungual surface, buttocks and anus. Lesions arising on the mucous membranes or torso are exceptional. Intra-oral architecture is rarely involved although intra-oral keratoacanthoma is common in male subjects [1].

Mean period of disease progression is at an encountered 15.1 months although 73.3% instances delineate an expeditious progression within < 3 days. Progressive tumours depict enhanced cellular proliferation and simulate a squamous cell carcinoma.

Subungual keratoacanthoma, denominated as solitary distal digital keratoacanthoma, is an exceptional and aggressive variant. The disorder is elucidated in young or middle aged Caucasian males commonly on the first three fingers of the hand.

Subungual keratoacanthoma manifests as a swiftly evolving lesion with consequent devastation of the bony substratum and infiltration of deep-seated soft tissues besides implication of non hair-bearing regions, contrary to adjunctive variants of keratoacanthoma with spontaneous resolution in exceptional instances. A history of precedent trauma can be cogitated. Preliminary lesions of subungual keratoacanthoma can induce onycholysis which simulates conditions such as onychomycosis. Radiographic imaging of the concerned digit is mandatory to discern osteolysis secondary to emergence of subungual keratoacanthoma [4,5].

Giant keratoacanthoma is an exceptional variant which exceeds a magnitude of 2 centimetres and appears with excessive sunlight exposure. Giant keratoacanthoma of head and neck is common in males and currently demonstrates a mean magnitude of 3.93 centimetres. The lesion is frequent in sixth to seventh decade with a mean age of appearance at 59.1 years.

Keratoacanthoma appearing in the head and neck can display a potential for distant and loco-regional metastasis.

Appearance of metastasis is signified with an aggressive biological countenance observed in lymph nodes, lungs and mediastinum. Enhanced cellular proliferation is cogitated in tumour progression with amplification of invasive characteristics as elucidated in squamous cell carcinoma.

Keratoacanthoma is commonly monitored for a mean duration of 56.65 months with a range extending from 2 months to 240 months. Biological pattern of infrequent giant keratoacanthoma in the head and neck is incompletely elucidated [5,6].

Clinical elucidation

Tumefaction emerges as an exophytic, violaceous, brownish or mildly reddish, painless, pedunculated nodule with superficial verrucae, a normal circumscribing skin or mucosa and absent lymph node metastasis. Miniature, round, pinkish or skin coloured papules, typically one to two centimetres in magnitude, which quickly progress to dome shaped nodules or buds with centric keratin filled crater or ulcer are exemplified. Antecedent lesions are miniature, reddish macules which evolve into firm papules, enlarge briskly in approximately 4 weeks to 8 weeks and eventually appear as hemispheric, firm, dome shaped, asymptomatic nodules.

Exclusion of tumour invasion and metastasis necessitate a detailed lymph node evaluation.

Dermoscopic analysis can be inadequate in suitably differentiating the lesions of keratoacanthoma or squamous cell carcinoma. However, it can discriminate the aforesaid lesions from adjunctive non pigmented skin conditions with epithelial elevations. Aspects such as blood spots, keratin and especially white circles are beneficial in discerning and categorising the lesion [6,7].

Histological elucidation

Excision biopsy is considered appropriate as a shave biopsy can be inadequate in assessing the depth of lesion and suitably distinguishes amidst keratoacanthoma and squamous cell carcinoma.

Islands composed of enlarged keratinocytes configuring invaginations of squamous epithelium and quantifiable central keratin are cogitated. Variable epidermal extensions protrude extensively into the dermis. Lymphocytic infiltration of the tumefaction is observed.

Morphology of keratacanthoma is contingent to the age of individual and stage of disease progression. Antecedent lesions enhance expeditiously with appropriate cellular differentiation and an augmented proliferation index. Attributes such as atypical mitosis, loss of polarity, individual cell keratinization and hyperchromatic cells can appear at delayed stages Histology of keratoacanthoma simulates a squamous cell carcinoma. Critical microscopic aspect is the rapid and precipitous transformation to epithelial hyperplasia. Full fledged keratoacanthoma comprises of a centric corpus of keratin encompassed with a concentric collar of skin or elevated mucosa with an erythematous perimeter [7,8].

Eruptive variant of the lesion is frequently devoid of centroidal keratin filled crater and clinically simulates an ulcerated neoplasm.

Morphological enunciation depicts a proliferation of well differentiated keratinocytes with adequate circumscription. Lesions demonstrate a multi-lobular, exophytic or endophytic pattern or cyst like invaginations of superimposed epidermis. Epidermal extension is cogitated beyond the tumour with an accompanying centralised, keratinous horn plug. Keratin filled crater margin is enveloped with projections of superficial stratified squamous epithelium. Neutrophilic micro-abscesses are demonstrated in the intra-epidermal region in addition to horn cysts. Keratoacanthoma is comprised of enlarged or atypical keratinocytes with an eosinophilic cytoplasm.

Morphology of solitary keratoacanthoma can vary amidst diverse stages. Contemporary classification of keratoacanthoma refers to the lesions as squamous cell carcinoma- keratoacanthoma (SCC-KA) [8,9].

Differential diagnosis

Keratoacanthoma necessitates a demarcation from squamous cell carcinoma, amelanotic melanoma, molluscum contagiosum, prurigo nodularis, metastatic lesions to the skin, merkel cell carcinoma, nodular and ulcerative variants of basal cell carcinoma, nodular Kaposi's sarcoma, hypertrophic lichen planus, deep-seated fungal infection, atypical mycobacterial infection, foreign body reaction and verruca vulgaris [1].

Morphological criterion favouring keratoacanthoma include a distinctive epithelial margin with divergent tumour and stroma and foci of ulceration. Morphological parameters defining a squamous cell carcinoma include innumerable mitotic figures and prominent cellular pleomorphism.

Biomarkers defining epidermal differentiation and intracellular adhesion can be utilized to distinguish amidst keratoacanthoma and squamous cell carcinoma. Immune staining with filaggrin is intense in keratoacanthoma. Mature lesions of keratoacanthoma can elucidate vascular cell adhesion molecule (VCAM), intercellular cell adhesion molecule (ICAM), Syndecan-I and E- cadherin whereas immune reaction to aforesaid molecules is focal in squamous cell carcinoma. Elevated anti-apoptic protein markers such as Bcl2 are commonly delineated in squamous cell carcinoma [1,2]. Keratoacanthoma is contemplated in the differential diagnosis of ulcerated skin lesions depicting circumscribed and convoluted tumour margins and a keratinized centric zone on histology, irrespective of the location of the lesion.

Clinical and histological distinction of subungual keratoacanthoma is with squamous cell carcinoma. Subungual lesions are exophytic with an expeditious tumour evolution. Squamous cell carcinoma generally appears in elderly patients, progresses surreptitiously with a deceptive external appearance. Osteolysis can ensue in subungual keratoacanthoma on account of pressure and is sharply defined, in contrast to poorly defined osteolytic foci cogitated in squamous cell carcinoma due to direct infiltration of the bone accompanied by periosteal thickening and reactive sclerosis [9,19].

Typical morphology of subungual keratosis displays hyperkeratosis, parakeratosis, centrally situated keratin filled crater, eosinophilic cells with dyskeratosis and minimal nuclear atypia. Architectural attributes are cogent and diagnostic of subungual keratoacanthoma whereas in squamous cell carcinoma cytological anomalies, mitotic figures, prominent cellular and nuclear atypia are considered diagnostically appropriate.

Elucidation of p53 and Ki67 is beneficial in discerning betwixt the particular tumefaction. Immune reactivity to p53 and Ki67 is focal and basal in subungual keratoacanthoma, in contrast to a disseminated epidermal staining discerned in subungual squamous cell carcinoma [10,11].

Therapeutic options

Pertinent therapy is recommended on account of possible emergence of a squamous cell carcinoma. Keratoacanthoma can persist with perpetually enlarging tumour thus a surgical excision is advocated.

Surgical excision with a perimeter of normal tissue of 4 millimetres is considered optimal. Lesions situated on the extremities which are beneath < 2 centimetre dimension can be managed with electrodessication and curettage. Aggressive, enlarged tumours exceeding 2 centimetre diameter, situated in cosmetically sensitive sites necessitate tissue sparing surgical procedures and Moh's microsurgery is contemplated as a cogent option.

Non-surgical therapeutic options incorporate the application of 5% topical imiquimod cream, topical 5% 5 fluorouracil (5FU) cream, intralesional methotrexate injections, intralesional bleomycin, intralesional interferon alpha 2a, intralesional 5 fluorouracil and oral isotretinoin. Intralesional therapy with 5 fluorouracil and methotrexate are frequently employed. An estimated 98% response rate is enunciated with 5 fluorouracil. Intralesional methotrexate depicts a tumour regression rate of 83% to 100% [11,12].

On account of tendency of keratoacanthoma to spontaneously regress, several methodologies are offered to alleviate the lesion although assessment of efficacy of certain modalities is challenging. Lesion can invade abutting soft tissue with aesthetic consequences, particularly in instances devoid of therapeutic intervention.

As giant keratoacanthoma of head and neck displays an aggressive clinical course, surgical extermination is a frequently employed modality (291.1% instances), followed by concordant surgery and irradiation (8.3% instances). Tumour retrogression is elucidated, excluding instances subjected to electrodessication and curettage with radiotherapy and bleomycin [12,13].

Subjects offered surgical therapeutic options enunciate reduced span of treatment with quicker alleviation, whereas individuals on intra-lesional therapy necessitate multiple injections of therapeutic agents with consequent extended follow up. Typically, lesions of keratoacanthoma can resolve spontaneously with subsequently delayed reappearance. Spontaneous retrogression of lesion can appear in 4 months to 6 months with a minuscule residual scar.

Cryosurgery is an efficacious technique for managing benign skin conditions, particularly in the Caucasian population and in lesions confined to non-hair bearing zones. Spray or timed out spot freeze technique, rotary or spiral pattern and paint brush methodology are suitable. Benign skin lesions which can be appropriately managed with cryosurgery include actinic keratosis, solar lentigo, seborrheic keratosis, viral wart, molluscum contagiosum and dermatofibroma. Cryosurgery is an inexpensive, quickly performed office procedure devoid of anaesthesia or suture placement with a minimal time for preparation, minimal risk of infection and minimal deliberation to the wound. Complications of cryosurgery include haemorrhage, blister formation, headache, loss of hair, hypo-pigmentation and infrequent scarring [2,3].

Skin lesions usually mandate a singular session although for a few lesions several sittings are a pre-requisite. Methodology of cryotherapy includes the application of liquid nitrogen and is contingent to factors such as heat transfer, cellular injury with damaged cell wall and inflammation on account of local cell destruction. Cryotherapy is suitable for superficial lesions and as an adjuvant therapy to surgical manoeuvres. An augmentation of the freezing time is mandated in keratoacanthoma on account of ascending and descending tumour progression. Keratoacanthoma is usually managed with active therapeutic intervention, in contrast to a policy of "watchful waiting" cogent for spontaneous retrogression.

Benign subungual keratoacanthoma is appropriately managed with conservative therapy. Surgical excision or a localized administration of methotrexate can be contemplated. Amputation is a preferred option for multiple reoccurrences or for instances with a debatable distinction from squamous cell carcinoma.

Tumour recurrence can be associated with human immune deficiency (HIV) virus induced immune suppression. Infection with HIV is deliberated as a probable factor in the progression of keratoacanthoma. Lesions accompanied with HIV display an aggressive clinical course thus close monitoring is a pre-requisite. Surgical extermination of keratoacanthoma is followed by a superior prognosis. Subjects with keratoacanthoma are contingent to sun exposure and require adequate monitoring for the emergence of recent, contemporary, primary skin malignancies. Metastasis is infrequent though may appear with perineural dissemination [13,14].

Ferguson-Smith	One to several nodules in succession, benign in adolescence
Grzybowski	1 - 5 mm follicular papules in adulthood, eruptive and progressive, heal without scarring
Witten Zak	1 - 5 mm follicular papules and larger nodules, benign in adulthood
Muir-Torre	Association of ≥ 1 sebaceous neoplasm or ≥keratoacanthoma with internal malignancy
Incontinentia pigment	Subungual tumours
Xeroderma pigmentosum	Initial Blaschkoid blisters, verrucous lesions, hyperpigmentation, eventful hypopigmentation with early development of cutaneous cancers

Table: *Disorders with Keratoacanthoma [3].*

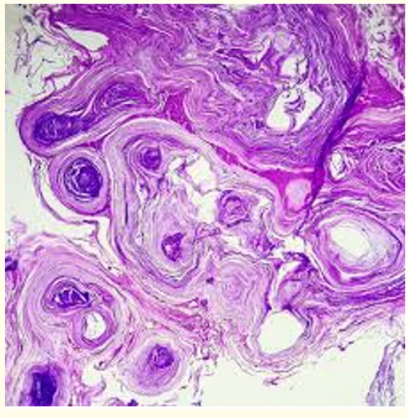

Figure 1: *Concentric horn pearls with an epithelial perimeter-keratoacanthoma [15].*

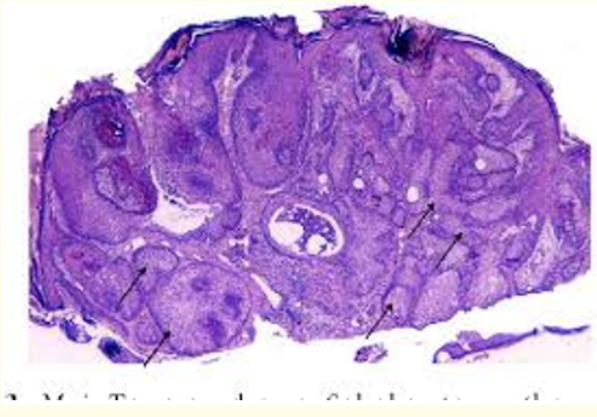

Figure 2: *Keratinous horn cysts with foci of sebaceous differentiation in a keratoacanthoma as a component of a Muir-Torre syndrome [16].*

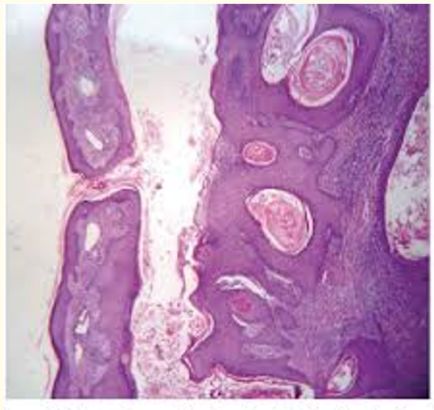

Figure 3: *Epithelial hyperplasia with focal and centric keratinous aggregates in a keratoacanthoma [16].*

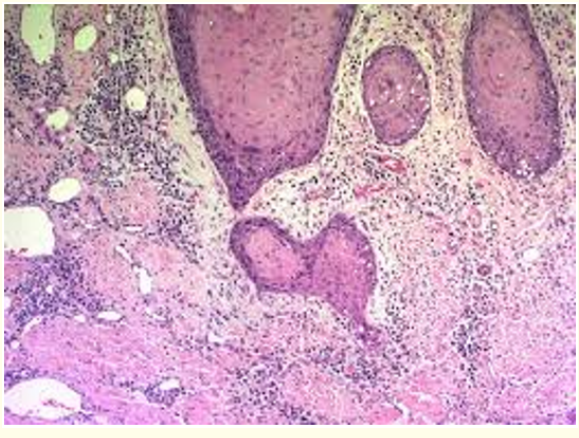

Figure 4: *Descending epithelial hyperplasia with focal lymphocytic infiltrate and clusters of enlarged keratinocytes in a keratoacanthoma [17].*

Figure 5: *Crater of keratinous deposit surrounded by extensive epithelial hyperplasia and focal chronic inflammation in a keratoacanthoma [18].*

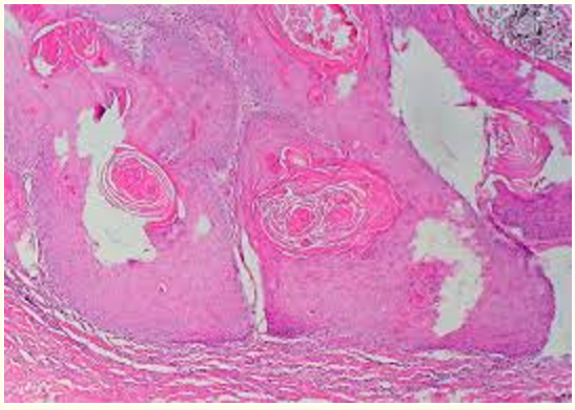

Figure 6: *Keratoacanthoma with dense accumulation of keratinous debris and circumscribing epithelial accumulations [19].*

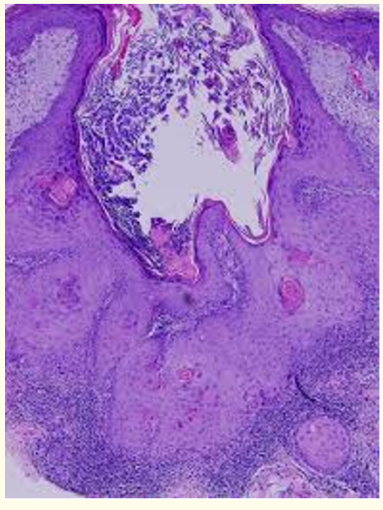

Figure 7: *Centroidal crater with flakes of keratin with encompassing extensive epidermal hyperplasia in a keratoacanthoma [20].*

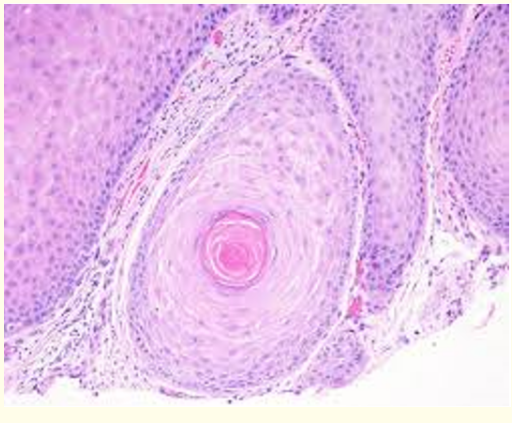

Figure 8: *Keratoacanthoma with a centric keratin filled horn cysts and an enveloping stratified squamous epithelium [20].*

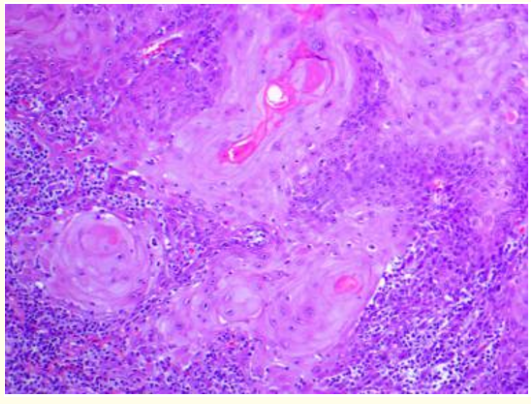

Figure 9: *Keratoacanthoma with keratin aggregates and encircling squamous epithelial projections [21].*

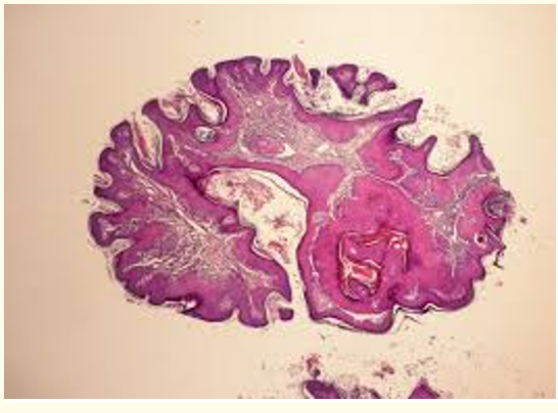

Figure 10: *Whole mount view of keratoacanthoma with epithelial convolutions and keratinous accumulation in a crater [22].*

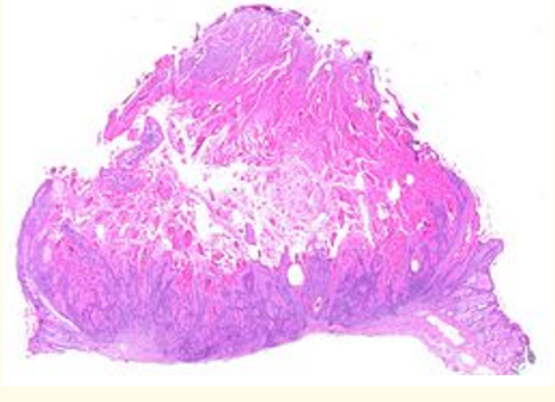

Figure 11: *Whole mount view of a keratoacanthoma with pivotal keratin and circumventing epithelial prolongations [23].*

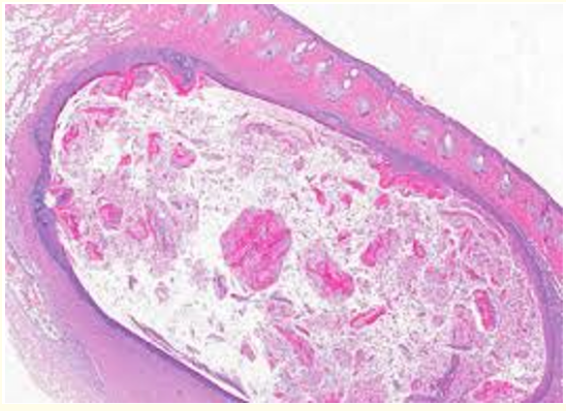

Figure 12: *Keratoacanthoma with keratin in a cystic cavity with layered stratified squamous epithelium [24].*

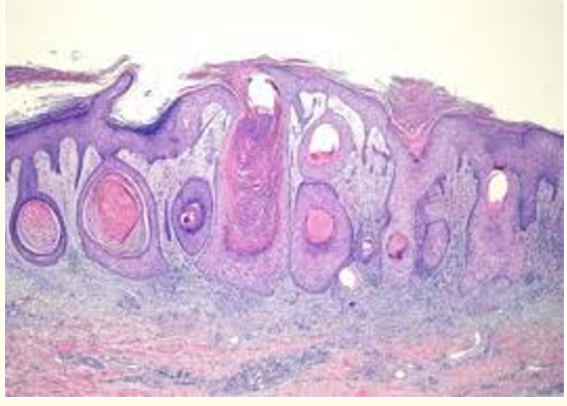

Figure 13: *Keratocanthoma with innumerable horn cysts and superimposed stratified squamous epithelium intermingled with a dermal lymphocytic infiltrate [24].*

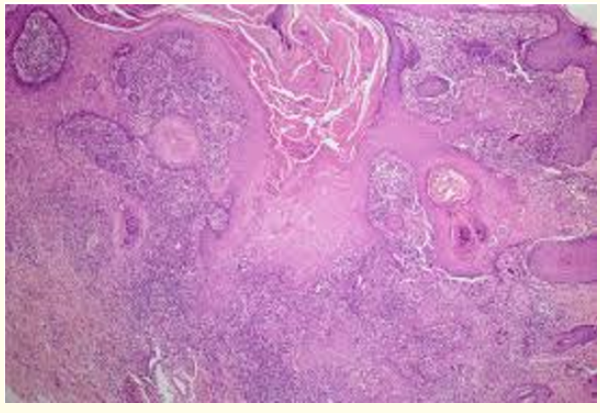

Figure 14: *Keratoacanthoma with bulbous keratinous assemblage and protrusions of stratified squamous epithelium and lack of atypia [20].*

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15. Image 1 Courtesy: Picoku.net.

16. Image 2 and 3 Courtesy: Semantic scholar.

17. Image 4 Courtesy: Skinolwin.com.

18. Image 5 Courtesy: shvpl.com images and suggestions.

19. Image 6 Courtesy: Wikimedia commons.

20. Image 7, 8 and 14 Courtesy: escholarship.com.

21. Image 9 Courtesy: movie web.

22. Image 10 Courtesy: Rock café.

23. Image 11 Courtesy: Libre pathology.

24. Image 12 and 13 Courtesy: Science direct.

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