

## Exo-Endophytic Eddies: Inverted Follicular Keratosis

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### Mini Review

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### Abstract

Inverted follicular keratosis is denominated as an infrequent, benign neoplasm engendered from hair follicular infundibulum. Although a neoplasm of indeterminate genesis, inverted follicular keratosis can be considered as a variant of seborrheic keratosis. Inverted follicular keratosis describes chromatic variants on account of cellular content incorporated with melanin, particularly with brown and yellow discoloration. Secondary degeneration of the lesions is extremely exceptional.

**Keywords:** Seborrheic Keratosis; Imiquimod

**Abbreviations:** HPV: Human Papilloma Virus; ISU: In Situ Hybridization.

### Introduction

#### Disease Characterization

Inverted follicular keratosis is contemplated as a variant of seborrheic keratosis. Alternatively, the condition can be cogitated as a virally induced epithelial hyperplasia with follicular configuration [1,2].

Inverted follicular keratosis is a gradually progressive neoplasm of follicular origin. Of obscure aetiology and pathogenesis, the tumefaction characteristically depicts an exo-endophytic pattern of tumour evolution. Middle aged to elderly individuals are commonly implicated with a male predominance and a male to female ratio at 2:1. Viral warts, seborrheic keratosis, viral infection (HPV) and Cowden's syndrome can be implicated in the pathogenesis of inverted follicular keratosis. Human papilloma virus (HPV) infection can concur with inverted follicular keratosis. An association with viral warts or seborrheic keratosis can be delineated although inverted follicular keratosis remains a distinct entity.

Generally elucidated in a singular fashion, inverted follicular keratosis can be concordant with disorders such as multiple acral keratosis, particularly in subjects with Cowden's syndrome [2,3].

#### Clinical Elucidation

Lesions appear as solitary, asymptomatic, firm, compact, non-pigmented, well demarcated, elliptical or spherical, flesh coloured, grey, white, tan, pink or brown verrucous plaques or papules of up to 1 centimetre magnitude. Nodules and plaques vary up to 5 centimetres with surface ulceration, are preponderantly delineated on the face, upper lip, cheeks or eyelids and can occasionally undergo spontaneous retrogression. Gradually progressive lesions can present with persistent otorrhoea, haemorrhage of verrucous lesion and partial obstruction of the surrounding viscera. Computerized tomography can depict the presence and extent of a soft tissue mass [3,4].

Head and neck (90%) is frequently incriminated particularly the chin, upper lip or face. Inverted follicular keratosis can appear in exceptional locations such as the

external auditory canal or eyelids and a histological assessment is consequently mandated.

Discernment of inverted follicular keratosis is preponderantly morphological as a clinical distinction from condition such as viral warts, seborrheic keratosis, actinic keratosis, basal cell carcinoma and squamous cell carcinoma is a challenging task [3,4].

### Histological Elucidation

Inverted follicular keratosis can be distinguished from adjunctive pathologies with specific morphological attributes. Nodules demonstrate a keratotic external surface. Typically, an admixture of endophytic and exophytic configuration of lesion is cogitated, denominated as an endo-exophytic pattern. Singular exophytic evolution of the tumour is also observed.

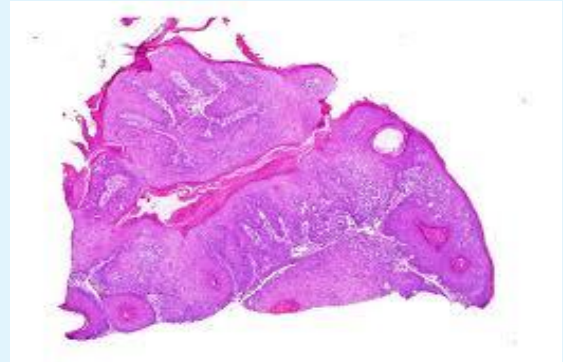
Hyperparakeratotic cutaneous lesions demonstrate an endophytic cellular proliferation chiefly comprised of basaloid and squamous cells. Additionally, exophytic and endophytic proliferation of squamous epithelial and basaloid cells is cogitated. Hyperkeratosis, parakeratosis and acanthosis of the superimposed epidermis is predominant [4,5]. Squamous eddies are focal and areas of pseudo invasion can be discerned. However, perimeter of the neoplasm is devoid of specific cellular infiltration.

Irregularly distributed aggregates of basaloid epithelium with peripheral palisading of basophilic nuclei are detected within the superficial dermis. Tumour cell nests and peri-tumoural stroma lack the presence of circumscribing clefts and spaces.

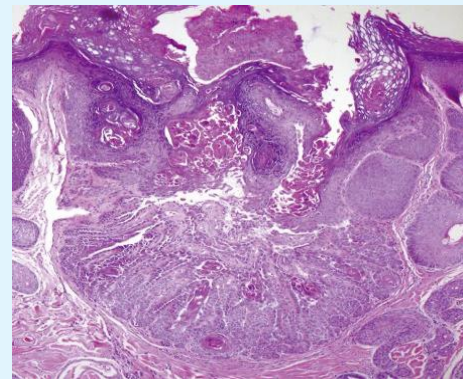
The neoplasm is characterized by enlarged lobules comprised of aggregates of peripheral basaloid cells and centroidal keratinized squamous epithelial accumulations with scaly swirls configuring the characteristic “squamous eddies”. Whorls of squamous epithelial cells with consequent keratinisation and production of keratohyaline granules or centroidal keratin spots constitute squamous eddies. Lobules commonly display filiform extensions with dermal projections comprised of tumour cells. Epithelial modifications such as occasional keratotic plugs can be enunciated. Koilocytic atypia or epithelial dysplasia is absent [5,6].

Basaloid cells are constituted by reactive or metamorphosed squamous epithelial cells and are implicated in the configuration of squamous eddies. Mitotic figures and a dense peri-follicular lymphoid and histiocytic inflammatory infiltrate is elucidated with a

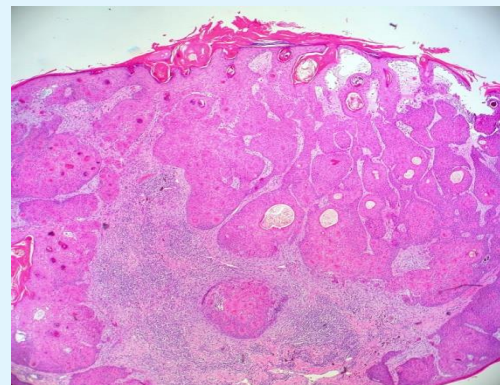
pseudo infiltrative articulation. However, an apparent stromal invasion or stromal desmoplastic reaction is absent [6-10] (Figures 1-11).



**Figure 1:** Squamous eddies, basaloid aggregates and follicular pattern in inverted follicular keratosis [11].



**Figure 2:** Basaloid aggregates, acanthotic, hyperkeratotic epithelium and perifollicular inflammation in inverted follicular keratosis [12].



**Figure 3:** Follicular dissemination of basaloid cells with perifollicular inflammatory clusters in inverted follicular keratosis [13].

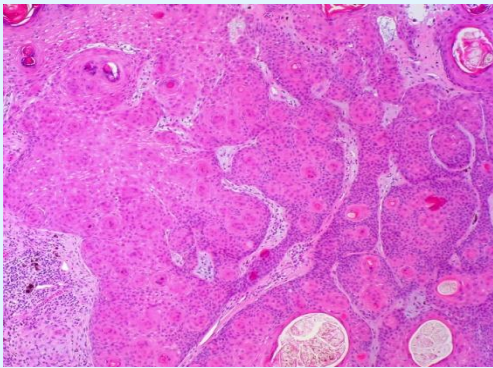


Figure 4: Squamous eddies, follicular configuration and dykeratotic epithelium in inverted follicular keratosis [13].

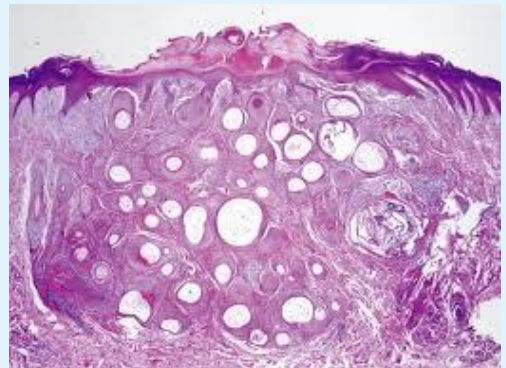


Figure 7: Clusters of dyskeratotic keratinocytes with superimposed hyperkeratotic and acanthotic epithelium in inverted follicular dyskeratosis [16].

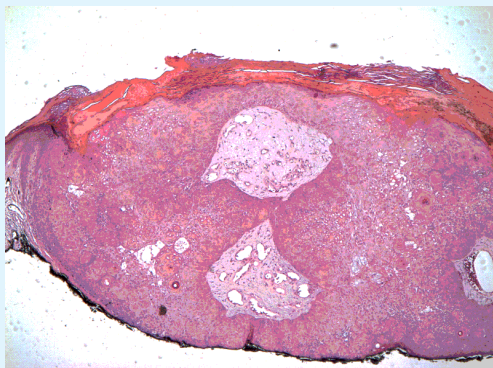


Figure 5: Aggregates of anomalous keratinocytes with lack of epithelial dysplasia in inverted follicular keratosis [14].

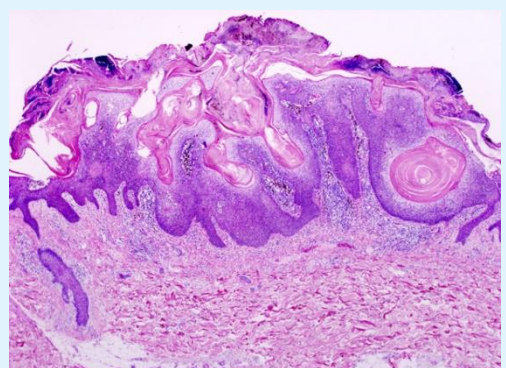


Figure 8: Squamous eddies, hyperkeratosis, parakeratosis, acanthosis and uninvolved superficial epithelium in inverted follicular keratosis [16].

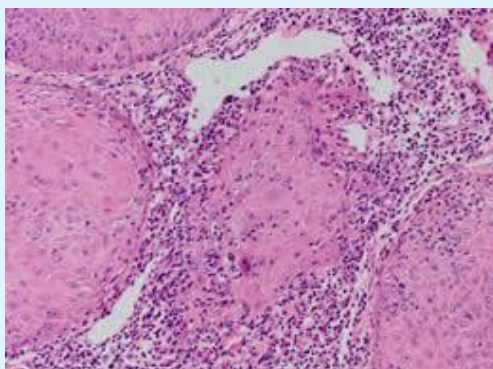


Figure 6: Squamous eddies, dyskeratotic keratinocytes with lymphocytic infiltration in inverted follicular keratosis [15].

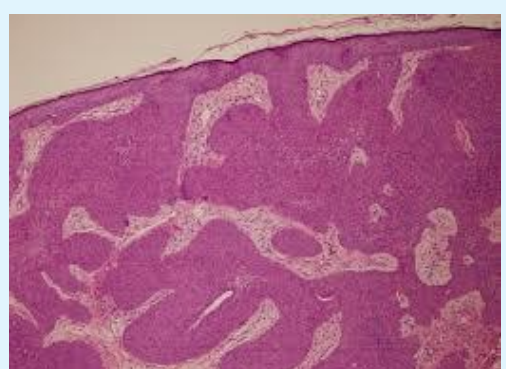


Figure 9: Basaloid accumulations with follicular architecture and minimal perifollicular inflammation in inverted follicular keratosis [16].

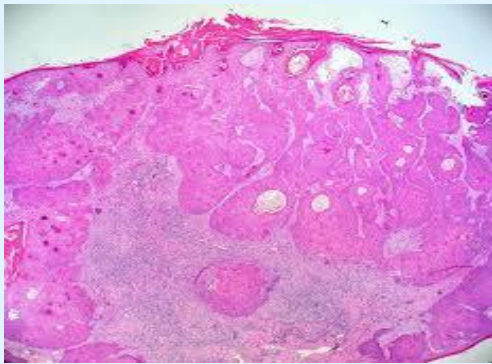


Figure 10: Squamous eddies, dyskeratotic keratinocytes and dermal lymphocytes in inverted follicular keratosis [16].

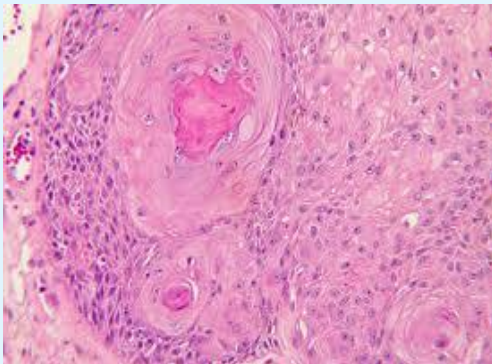


Figure 11: Squamous eddies and aberrant keratinocytes in inverted follicular keratosis [17].

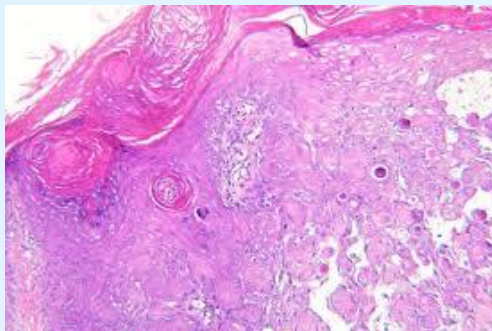


Figure 12: Squamoid follicles, eddies and keratinous granular cells in inverted follicular keratosis [17].

### Immune- Histochemical Reactions

Immune histochemical reactivity for human papilloma virus (HPV) is absent in inverted follicular keratosis.

Epidermal dendritic cells immune reactive to BCL2 can be discerned in inverted follicular keratosis, though are absent in squamous cell carcinoma or seborrheic keratosis.

Superficial epithelium of inverted follicular keratosis is immune reactive to calretinin which commonly immune-stains the inmost coating of outer root sheath of hair follicles. Application of in situ hybridization (ISH) and immune histochemistry for human papilloma virus (HPV) assist the diagnosis [7,8].

### Differential Diagnosis

Demarcation of inverted follicular keratosis from conditions such as viral warts, seborrheic keratosis, actinic keratosis, basal cell carcinoma and squamous cell carcinoma is mandated.

Clinical segregation of inverted follicular keratosis from conditions such as viral warts, basal cell carcinoma or squamous cell carcinoma can be challenging as aforesaid disorders typically demonstrate a keratinized epithelial proliferation. However, lesions of squamous cell carcinoma lack an adequately demarcated perimeter, atypical mitosis, cellular atypia and are devoid of squamous eddies [8,9].

Segregation of inverted follicular keratosis from "irritated" variant of seborrheic keratosis can be challenging as the dual conditions recapitulate associated benign and malignant disorders. Lesions of irritated variant of seborrheic keratosis are elevated at the edges beyond the enveloping skin and are commonly devoid of an endophytic component.

Dermatoscopy is an ineffective technique for discerning inverted follicular keratosis and its segregation from frequent pathologies such as viral warts, seborrheic keratosis, basal cell carcinoma and squamous cell carcinoma [9,10].

### Therapeutic Options

Frequent and preferred therapeutic modality for managing inverted follicular keratosis is a comprehensive surgical elimination.

Imiquimod is an immune-modulatory agent frequently employed in treating actinic warts, genital warts, superficial lesions of basal cell carcinoma and several associated reactive dermatological disorders or neoplasm. Therapeutic agent imiquimod modifies and up-regulates the immune system. The drug displays anti-cancerous and

antiviral functions. Imiquimod activates the immune system and induces cytokine production from antigen presenting cells such as monocytes, macrophages and dendritic reticulum cells including toll like receptors (TLR) 7 and 8. Topical administration of imiquimod prohibits genesis of vascular tumours by reducing proliferation of tumour cells, enhancing apoptosis and engendering a decline in the activity of matrix metalloproteinases 1 and 9. Topical application is tolerated well with the induction of minimal complications such as localized skin reaction at the site of application [5].

Subsequent to surgical eradication, the neoplasm is devoid of infiltrative tumour evolution or metastasis. As the tumefaction lacks a malignant transformation, additional treatment remains unnecessary [9,10].

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