

THE INVERTED FOLLICULAR KERATOSIS

A Surprising Variant of Seborrheic Wart

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Abstract. The pathological features of 29 lesions that had been diagnosed as inverted follicular keratoma have been reviewed. The clinical data suggest that these lesions occur predominantly on the face of middle-aged or elderly man. None were correctly diagnosed before removal. The main histological points noted were the presence of an invaginated type of architecture, foci of keratinization (squamous eddies) and areas of basaloid cells which were arranged haphazardly with mitotic figures (Borst-Jadassohn change). All the histological features seen are also observed in irritated or traumatized seborrheic warts and no evidence was found for the original suggestion that these lesions derive from hair follicles.

Key words: Skin; Pathology; Benign epithelial tumour

Seborrheic warts have been recognised as benign tumours for nearly a century (1, 13). Pringle (15) stressed their benignity but considered that malignant transformation occasionally occurred, a view sustained by Sachs et al. (16) and by Sutton (20). Few pathologists or dermatologists now believe that this is the case (19).

The histological variability of this common lesion is astonishing and many tumours that were initially thought to be distinct entities have eventually become accepted as variants of the seborrheic wart. Amongst these are the granuloma senile (6), the basosquamous cell epidermal tumour (8) and the melano-acanthoma (12). Schnyder (18) describes this lesion fully in the section of his book dealing with benign epithelial tumours.

It is the purpose of this paper to report a study of the condition known as inverted follicular keratosis (IFK) (5) and to reinforce previous suggestions that it should be recognised as yet another variant of the seborrheic wart.

PRESENT SERIES

The present series comprises 29 cases, 26 of which were found in a review of the histological material at the Institute of Dermatology, London, over the 10-year period 1963-73 and 3 others prior to that. The majority of the patients with these lesions had attended St. John's Hospital for Diseases of the Skin but the series includes 4 cases whose histological material was referred to the Institute from other hospitals and whose clinical notes were available to us.

Criteria for acceptance

Cases were included in the series if the histological sections from the lesions showed most of the following features: that

- (i) the epidermal tumours showed no adnexal differentiation,
- (ii) there was an invaginated or inverted type of architecture in which the body of the lesion lay well below the surface of the surrounding epidermis,
- (iii) there were whorls of maturing squamous epithelium within the body of the lesion (squamous eddies),
- (iv) there were horn cysts or keratin-filled crypts within the body of the lesion,
- (v) there were many mitotic figures,
- (vi) there was a pronounced inflammatory cell infiltrate.

HISTOLOGICAL FINDINGS

In general the bulk of these lesions lay below the surface of the skin. However, complete invagina-

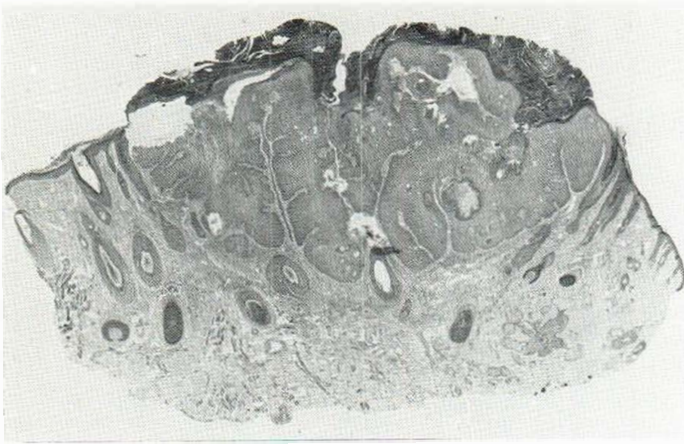


Fig. 1. Overall view of lesion of IFK, showing a lobulated epithelial mass predominantly below the skin surface. H&E, $\times 3$.

tion was not always present. Nineteen cases showed the typical inverted type of architecture but in those 10 in which it was less obvious, other cardinal features including squamous eddies, horn cysts, mitotic figures and an inflammatory infiltrate, were found (Figs. 1, 2). A connection with hair follicles was only rarely demonstrated. In the 2 cases in which the hair follicles appeared to be incorporated into the base of the lesion, one had an inverted architecture and the other an architecture more like that of a seborrheic wart. In 7 cases hair follicles were close to the base of the lesion but not contiguous with it (as might be expected in random biopsies of facial skin). In 14 others there was no evidence of pilosebaceous elements at the base. In 8 cases the lesion was incomplete at the base and it was impossible to tell whether hair follicles were related or not. The bulk of each lesion was composed of immature keratinocytes resembling, on the whole, the basaloid cells of a seborrheic wart (Fig. 3).

Squamous eddies were present in all cases. These eddies consisted of flattened, more eosinophilic squamous cells surrounded by plumper, less keratinized cells, the whole structure being arranged in a whorled pattern (Fig. 4). The eddies were numerous in many instances; in some they were limited in number. However, there was no correlation between their frequency and the presence of other histological features. Eosinophilic and swollen cells with pyknotic nuclei were scattered through the lesion in 9 instances.

There were, in addition, islands of closely packed, small basaloid cells surrounded by larger, paler keratinocytes. Mitotic figures were some-

times prominent in these areas (18 of the 29 lesions) and in 5 were quite striking, there being five or six per high-power field (Fig. 5). In some areas groups of basaloid cells showed loss of polarity and



Fig. 2. Overall view of another IFK, lying partially below the skin surface. The epithelial mass is more tortuously arranged than in Fig. 1 and contains horn cysts ($\uparrow$). H&E, $\times 4$.



Fig. 3. Lobulated epithelial structure of IFK. The constituent cells vary but many are small and immature, as seen in a seborrheic wart. H&E, $\times 12$.

imperfect cohesion (Fig. 6). This separation of cells was noted in 13 cases in the series and in 3 was sufficiently pronounced to be regarded as acantho-

lysis. These features are sometimes seen within seborrheic warts and resemble the changes described as Borst-Jadassohn intra-epidermal epithelioma. Edema and disintegration of cells was seen in 4 cases, amounting to vesicle formation in one (Fig. 7).

The absence of pigmentation in the lesions was a notable feature in this series. Only two lesions were deeply pigmented; one of these was from a coloured patient, 4 more had moderate pigment but the majority (23 cases) had none detectable at all. An inflammatory infiltrate was present in all but 2 cases. The infiltrate was situated at the base or sides of the lesion but was also frequently seen invading the epithelial columns and this was a marked feature in 5 cases. The cell types were predominantly lympho-histiocytic in all cases, although polymorphonuclear leukocytes were seen in some. In 4, plasma cells were also plentiful and in one of these there were also numerous eosinophils. One case showed an aggregation of polymorphs amounting to a mini-abscess in the substance of the lesion.

In general these lesions were more 'warty' than seborrheic warts and several did have horny caps or frank horns. In 9 the surface horn was prominently parakeratotic. Four lesions showed many large dilated blood vessels.

CLINICAL DETAILS

The clinical characteristics of the 29 lesions reported and details of the patients were obtained retrospectively from the hospital case notes.



Fig. 4. Part of the epithelial mass of an IFK showing numerous foci of keratinization (squamous eddies). H&E, $\times 55$.

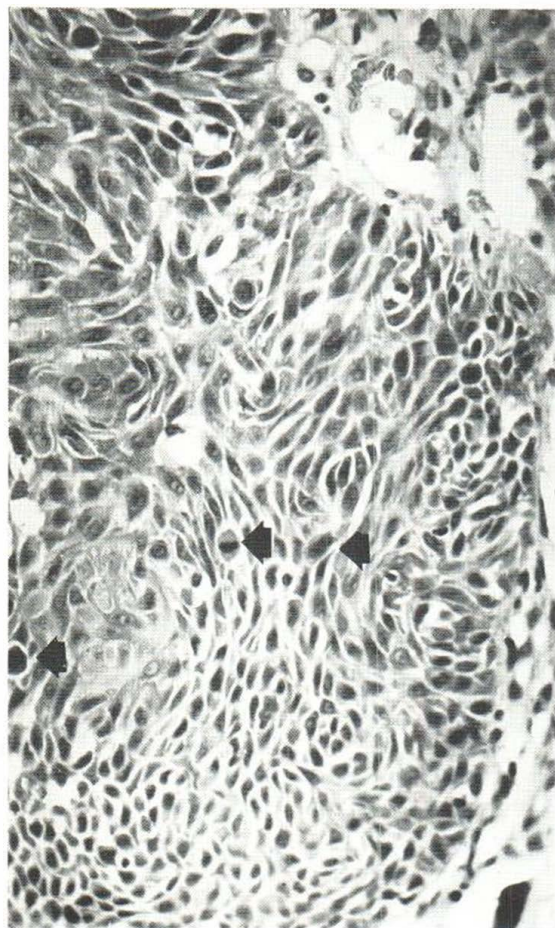


Fig. 5. View of part of a lesion with many mitotic figures. At least three are visible in this photomicrograph (↔) H&E, $\times 70$.

Race

All but 2 patients were white Caucasians. The age, sex and duration of lesion are given in Table 1.

Size

The size of the lesion was unrecorded or was described as small, in most instances. In those cases where exact measurements were given, 4 were 5 mm in diameter, 1 was 6 mm and 2 were 1 cm in diameter. Two were described as of split pea size.

Symptoms

The majority of cases were asymptomatic. Five patients complained that the lesion bled on occasion. Three of these patients had lesions on the

upper lip which were traumatised by shaving. The other 2 patients had lesions on the nose. One male patient with a post-aural lesion complained that it discharged and became inflamed.

CLINICAL DIAGNOSIS

The clinical diagnosis of IFK was not suggested by the clinician in any of the cases. In 2 patients who had seborrheic warts elsewhere, the lesion was diagnosed as a seborrheic wart. Thirteen cases were variously described as wart, warty nodule, warty papilloma, warty lesion, warty growth, verrucous papule, or papillomatous horn. Two were described as cutaneous horns. One was labelled papilloma, 2 as nodules, one as painless tumour, one as pearly tumour and another as pedunculated papule. One was diagnosed as a keratoacanthoma and another as ?KA ?wart. One was diagnosed as a rodent ulcer, one was called a warty naevus, one was thought to be a pyogenic granuloma and another a keratotic pyogenic granuloma.

RECURRENCE

One case required excision on two occasions but no other recurrences were reported. Nineteen patients who could be traced were asked by letter to attend

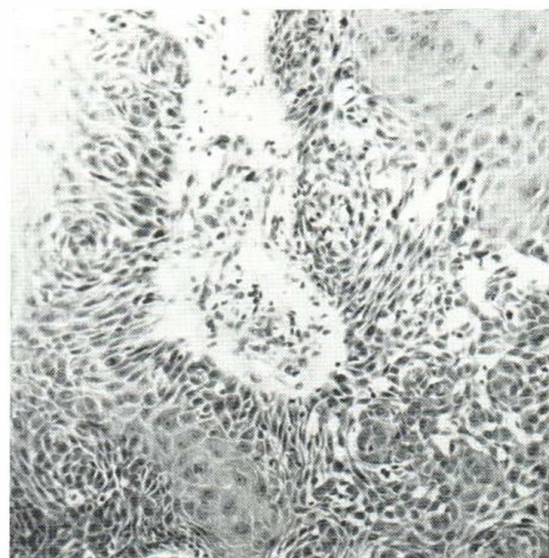


Fig. 6. There is considerable intercellular edema with separation of cells in this area of a lesion of IFK. H&E, $\times 68$.

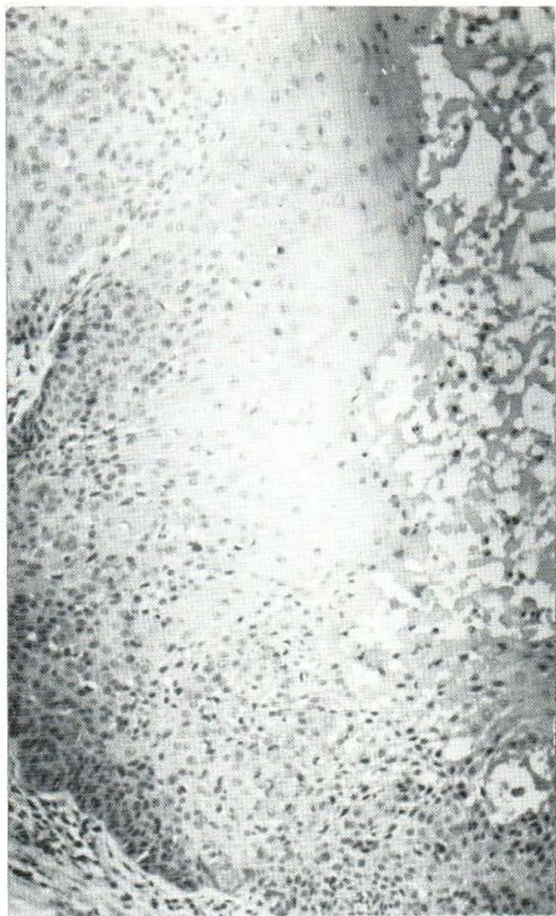


Fig. 7. Intracellular oedema and degeneration of cells is obvious in this lesion of IFK. H&E. $\times 72$.

for examination. Of the 10 who attended and were examined, all had healed satisfactorily following excision of the lesion between 2 and 7 years previously. There were no visible recurrences.

COMMENTS

In 1954 Helwig (15) described the clinical and histological features of a lesion to which he gave the name inverted follicular keratosis (IFK). In appearance they were small, single papulo-nodules with a papillary surface containing crypts and predominantly located on the face. The salient histological features were a cup-shaped inverted architecture containing a central cellular mass in which there were one or several depressions or crypts, considered by Helwig to be analogous to the opening of a pilosebaceous apparatus. He pointed out that

the cells of the mass varied—from those which were natural for a cell immediately above the basal layer, to mature keratinizing cells and that these latter cells formed a distinctive pattern which he termed "squamous eddies". Furthermore, the cells surrounding such eddies were somewhat flattened, as in the middle layers of the normal epidermis or wall of a hair follicle. Helwig stressed that the lesion was benign. Although mitotic figures were frequent they were normal and the transition of cells from basaloid to squamous was orderly, unlike that of squamous cell carcinoma. He considered that in contrast to seborrheic keratosis, the lesion of IFK often extends down to the underlying corium, whereas the former is characteristically located above the normal layer of the epidermis and contains numerous horn cysts. However, Helwig conceded that the distinction between the two could be difficult because an irritated seborrheic keratosis can also show the phenomenon of squamous eddies. Despite guarded misgiving, the concept of IFK as a distinct entity appears to have been accepted. Boniuk & Zimmerman (3) reported 64 cases of lesions of the eyelid and eyebrow under this title, though they emphasized that the majority of their cases did not have inverted cup-shaped configuration, nor did they accept Helwig's contention that the presence of keratin crypts is proof of the follicular origin of these lesions, but considered that the term IFK should be retained, since "it has gained some acceptance and since a more descriptive name is not available".

The clinical description of Boniuk & Zimmerman's cases was similar to that given by Helwig and, apart from the inverted architecture, so also were the histological appearances. They also recorded considerable inter and intracellular edema, as well as inflammatory cells (lymphocytes) at the base of the lesion—but no dyskeratosis. The authors also emphasised that pathological misdiagnosis of this lesion could be serious; they were able to find 17 cases of IFK in a series of lesions previously reported as being squamous cell epitheliomas.

Duperrat & Mascaro (4), reported 5 cases of a tumour with clinical and histological features similar to IFK and considered that the tumour is derived from the intra-epidermal portion of the hair follicle (acrotichium or infundibulum), and is thus analogous to the eccrine poroma as described by

Table I. Age and sex of patients and duration of lesion

	No. of cases
Sex incidence	
Males	21
Females	6
Age at excision (years)	
21-30	3
31-40	1
41-50	2
51-60	7
61-70	12
71-80	3
81-90	1
Duration of lesion	
3 months or less	13
3 to 6 months	5
6 to 12 months	4
Several months	1
One to twenty years	5
Unrecorded	1

Pinkus *et al.* (14). Mehregan (9) reported 40 cases of IFK and agreed that the tumour probably arises from the intra-epidermal portion of the hair follicle.

IS IFK A SEPARATE ENTITY?

Not all authorities accept that IFK is a separate entity. Bednar & Trapl (2) in a discussion of senile (seborrhoeic) verrucae considered that in addition to the basic form with evenly represented hyperkeratosis, acanthosis and papillomatosis, there are further variants where one of the signs predominates. Amongst these variants they listed the inverted form described by Helwig as IFK. Lever (7) also stated that it was likely that IFK represented an irritated seborrhoeic wart, since its major features are also seen in the latter condition.

The age distribution of patients in this series is similar to that of patients with seborrhoeic warts, i.e. a predominance in the fifth and sixth decades.

The site of all but five of the lesions was the face and scalp. Mehregan & Pinkus (10) also noted a similar distribution and believed that this supported a follicular origin of IFK, since the face is the commonest site of other tumours of follicular origin. It should be noted that the face is also a common site for seborrhoeic warts. It is of interest, however, that only two lesions were on the trunk, which is also a common site for seborrhoeic warts. There are two possible explanations for this discrepancy.

First, the greater likelihood that facial lesions are traumatised and irritated and hence excised for fear of malignancy and secondly, that facial lesions are noted by the patient at an early stage and excised for cosmetic reasons. However, follicular types of seborrhoeic warts do occur on the trunk (17). These show acanthosis in and around the sebaceous ducts but none of the other features of IFK or of irritated seborrhoeic warts. The histological features of IFK have all previously been noted in seborrhoeic warts which have been irritated in some way. Mehregan & Pinkus (10) in a detailed study of intra-epidermal epithelioma recorded 65 cases of seborrhoeic keratosis containing intra-epidermal nests; of these, 33 showed evidence of inflammation resulting in the formation of squamous eddies due to maturation of basaloid cells. Mevorah & Mishima (11) described the effects that experimental irritation produced on seborrhoeic warts. The histological changes which occur when a seborrhoeic wart is irritated may be summarized as follows:

1. Pseudo-epitheliomatous hyperplasia.
2. Changes in keratinization leading to the formation of squamous eddies and horn cysts which by coalescence form keratin-filled crypts. An increased production of parakeratotic horn.
3. The Borst-Jadassohn change with the formation of intra-epidermal collections of small basaloid cells, and lack of adhesion sometimes associated with inter and intra-cellular edema.
4. An increase in the number of mitotic figures.
5. A decrease in the production of melanin by melanocytes.
6. A pronounced inflammatory infiltrate at the base and sides of the lesion.
7. Increased PAS staining in some areas of the tumour.

Table II. Site of lesion

Site	Cases
Nose	7
Cheek	2
Upper lip	5
Peri-oral region	2
Peri-orbital region	4
Post-aural region	1
Scalp	2
Unrecorded	1
Limbs	4
Buttock	1

These changes were present in varying degree in the majority of lesions seen in this series, whereas a follicular connection was inconsistent and can also be shown to occur in seborrheic warts of the face lacking the other features, or irritation. Squamous eddies—a phenomenon of focal maturation of keratinocytes—was present in all the lesions that we report here, though variable in degree. Another feature frequently seen in our material was the presence of foci of basaloid cells often arranged without any particular orientation and possessing a surprising number of mitotic figures. Parakeratotic horn was present in a third of the cases, a feature noted by Mevorah & Mishima (11) in their series of experimentally irritated seborrheic warts, as was the lack of pigmentation. The majority of the lesions we examined (23 cases), had no pigment at all. Inflammation is a not-unexpected finding in irritated seborrheic warts. Only 2 cases failed to show any evidence of this. The inflammatory cellular infiltrate was situated mainly at the base or sides of the lesion or surrounding the lobules, but in 5 cases invaded the epithelial columns themselves. It is arguable whether the inflammatory infiltrate was the cause of the epidermal unrest or provoked by it. Similar inflammatory changes can be seen in senile keratoses, acanthomas and squamous cell epitheliomas.

The two features which might be considered most germane to a follicular origin of these lesions are an inverted architecture containing horn cysts and the presence of pilo-sebaceous elements at the base of the lesion. In 16 of the cases in this series there was an acceptable cup-shaped architecture, 3 more showed partial "inversion", and in 10 cases this feature was absent.

Pilosebaceous elements were present in 7 cases and were not present in 14 cases. In 8 cases the lesion was incomplete at the base. In 2, the lesion appeared to be arising from or incorporated with the hair follicle. One was typical in every way of an inverted follicular keratosis, but the other had an architecture similar in some respects to an ordinary seborrheic wart. That pilo-sebaceous elements should be present at the base of the lesion in a third of the cases in no way implies that the lesion is not a seborrheic wart, since seborrheic warts may arise from the epithelium of the pilo-sebaceous follicle as well as from surface epithelium; both have a common origin in the primary epithelial germ. Serial sections of non-inflamed

facial seborrheic warts may also show pilo-sebaceous elements at the base of the lesion.

It is suggested that facial seborrheic warts are more prone to irritation than seborrheic warts elsewhere and that those in male patients are particularly subject to trauma on the shaving area. In both sexes these facial seborrheic warts are excised when they are small and of recent onset, for cosmetic reasons.

We believe that there is no firm evidence which suggests that IFK derives from any part of the hair follicle. Their recognition is of importance as they are not infrequently misdiagnosed as premalignant or malignant lesions.

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