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CLINICAL INVESTIGATION

Periocular inverted follicular keratosis: a retrospective series over 17 years

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Abstract

Purpose To evaluate the demographic, clinical, and histopathologic characteristics of periocular inverted follicular keratosis (IFK), a very rare lesion with poorly defined characteristics.

Study design Retrospective case series.

Methods We evaluated 11 patients with clinically diagnosed IFK confirmed by histologic analysis. Data were collected on the patients' demographics, clinical presentation and course of the disease, signs and symptoms, location of the lesion, and outcomes of treatment.

Results The patients' mean age was 71 years (range, 32–91 years). Seven (64%) of the patients were female. Eight of the patients (72.7%) had no symptoms, two (18.2%) reported itching, and one (9.1%) had edema and bleeding of the lesion. The lesion affected the upper eyelid in 4 of the patients (36%), the lower lid in 3 of the patients (27%), and the inner canthus in 4 of the patients (36%).

Conclusions IFK has no specific clinical characteristic and thus requires histologic confirmation for its diagnosis and appropriate management.

Keywords Inverted follicular keratosis · Papilloma · Periorbital

Introduction

Inverted follicular keratosis (IFK), also known as basosquamous cell acanthoma, usually appears as a rare, small, solitary, papillomatous benign lesion on the head, face, or neck, and in some cases, in the periorbital region [1–4]. Over the last 30 years, 11 articles on periorbital IFK have been published, of which only 7 documented the lesion as being on the eyelids [5–10]. The lesion arises from the follicular infundibulum, above the sebaceous duct opening. However, the exact etiopathogenesis remains unknown. Some have postulated that the pathogenesis is related to viral warts, but the human papillomavirus has not been detected in most cases of IFK [9, 11–14]. Others believe that IFK could actually be an "irritated" seborrheic keratosis [15]. The lesion can be similar to squamous cell carcinoma or basal cell carcinoma [5, 16]. Hence, it is important to highlight some characteristics that may be useful in differentiating between these lesions. In the current study, we reviewed the characteristics of our cases to present the demographic, clinical, and histopathologic characteristics of IFK. To our knowledge, this series is one of the largest series of periocular IFK that has been described since 1979.

Patients and methods

We retrospectively evaluated patients with a histologically confirmed diagnosis of periocular IFK between 2000 and 2017 at Rio Hortega University Hospital, Valladolid, Spain. The institutional research board approved this study, and

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consent was waived owing to the retrospective nature of the research.

The survey included consecutive cases in which lesion removal was performed. All the surgeries were performed by 1 of 5 surgeons (specialist ophthalmologists, plastic or maxillofacial surgeons), and histopathology reports were dictated by specialist dermatopathologists. Clinical data were collected on patient age, sex, clinical diagnosis, and location and on how long the lesion remained in the periocular region. Data were also collected on the date of surgery, surgical technique, histopathologic finding, recurrence, and follow-up. Data were analyzed according to the frequency of occurrence.

Case series description

Eleven cases of IFK were evaluated. Table 1 presents the patients' details. The mean age of the study sample at excision was 71 years (range, 32–91 years). Seven (64%) of the patients were female. The majority of the patients (8 patients, 72.7%) had no symptoms related to the presence of the lesion, and only 2 patients (18.2%) reported itching, and 1 patient (9.1%) reported edema plus bleeding. None of the patients had any history of previous cutaneous pathology or lesions.

The lesion affected the upper eyelid in 4 patients (36%), the lower eyelid in 3 patients (27%), and the inner canthus in 4 patients (36%). The time of progression was less than 6 months in 2 patients (18%), 6 to 12 months in 3 patients (27%), and 12 to 24 months in 1 patient (9%). The clinical diagnosis was a "skin lesion" or cutaneous horn in 3 patients (27%); papilloma, wart, or cutaneous horn versus papilloma in 1 patient (9%); and keratoacanthoma or basal cell carcinoma in 1 patient (9%).

Histologically, the lesions were compatible with IFK, showing an endophytic growth pattern with a crater shape that penetrated to the papillary and reticular dermis, with lobules formed by basaloid and squamous cells together in concentric layers, with larger keratinizing or keratohyalin cells toward the center, and characteristic squamous eddies with remnants of pilosebaceous follicles (Fig. 1).

The treatment in 10 cases was excisional biopsy: 5 of the excisional biopsies (45.4%) were secondary intention healing; 4 (36.4%), direct closure; and 1 (9.1%), the flap technique. The surgical data were missing for the remaining 1 case. Local recurrence occurred in 1 case (9.1%); for that case, a new exeresis was performed, with a good response at the last follow-up.

Discussion

Inverted follicular keratosis is a very rare lesion, and even more uncommon on the eyelids. Over a period of 17 years, we observed only 11 cases, in other words, 0.6 cases a year at our center. To our knowledge, this is the largest case series of IFK of the periocular region conducted since 1979 [17, 18].

In our study, IFK occurred mainly in women (64%). However, others have reported a male predominance of 2:1 [4, 19]. The average age of our patients was 71 years, which is somewhat older than the mean age of 58.5 years reported in other case series (Table 2).

In our series, the lesion did not commonly occur at 1 particular site. Previous studies report that 22% of IFK cases

Table 1 Demographic and clinical characteristics of patients with periocular inverted follicular keratosis (IFK) at Rio Hortega University Hospital, Spain from 2000 to 2017

Patient	Age, y	Sex	Duration of lesion, mo	Symptom	Clinical diagnosis	Location	Type of surgery	Follow-up after surgery, mo	Recurrence
1	82	F	6	None	Skin lesion	LL	NA	6	No
2	58	F	NA	None	Papilloma	UL	Secondary intention	18	Yes
3	91	M	NA	None	Cutaneous horn	UL	Secondary intention	6	No
4	81	F	NA	None	Cutaneous horn	IC	Secondary intention	6	No
5	32	F	6	Itching	Wart	LL	Secondary intention	6	No
6	71	F	NA	None	Cutaneous horn vs papilloma	LL	Secondary intention	6	No
7	69	M	12	None	Basal cell carcinoma	IC	Direct closure	12	No
8	63	F	NA	None	Keratoacanthoma	UL	Direct closure	6	No
9	84	M	<6	Bleeding, edema	Skin lesion	IC	Direct closure	6	No
10	83	F	6	None	Cutaneous horn	UL	Direct closure	6	No
11	69	M	<6	Itching	Skin lesion	IC	Flap	12	No

LL lower lid, *UL* upper lid, *IC* inner canthus

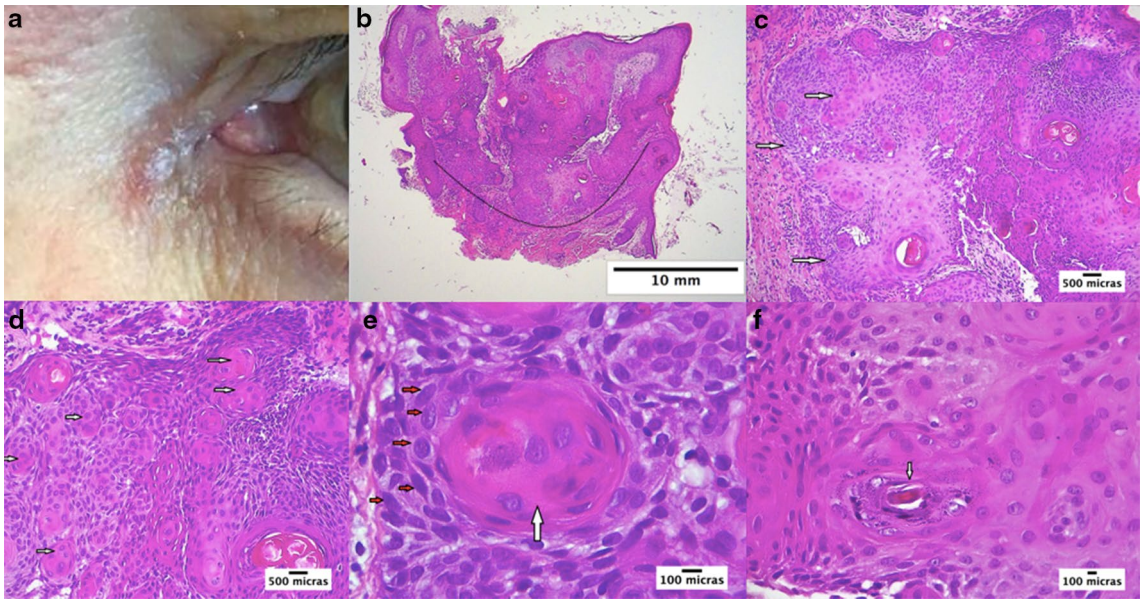

Fig. 1 **a** Clinical appearance of inverted follicular keratosis (IFK) showing a mild hyperemic area with vascularization in the inner canthus of the left eyelid. (**b**–**f**) Pathology slides of hematoxylin and eosin staining of IFK. **b** Endophytic growth lesion with a crateriform architecture affecting the reticular dermis. **c** The lesion has solid lobules, finger-like structures composed of squamous and basaloid cells (arrows). **d** Characteristic squamous eddies (white arrows). **e** Characteristic squamous eddies surrounded by basaloid cells (red arrows). **f** Hair follicle remnants (arrow) are a frequent finding in these lesions

occurred on the upper eyelid; 26%, on the lower eyelid; 3%, on the eyebrow; and 7%, in the periorbital region, but data were not available in 41% of the patients reported in the literature (Table 2).

Clinical diagnosis alone is not recommended because IFK is a rare lesion with no specific findings. Previous studies have estimated that only 0% to 2% of cases can be correctly diagnosed before removal of the lesion [20, 21]. Additionally, the clinical appearance is difficult to differentiate from other keratinizing lesions such as viral warts, seborrheic keratoses, and adnexal tumors. Because of its fast growth, IFK is also difficult to differentiate from malignant tumors such as keratoacanthoma, squamous cell carcinoma, basal cell carcinoma, and melanoma [22–24]. To improve the clinical diagnosis, other examinations including dermatoscopic characterization and reflectance confocal microscopy have been suggested [22]. However, these modalities are not specific for IKF, and the differential diagnosis from malignant tumors remains tenuous at best [23].

The difficulty in clinical diagnosis makes histopathologic analysis fundamental for correct diagnosis. Several histopathologic variants of IFK exist, and all are related to different clinical types [22, 23]. In addition, a variable degree of hyperkeratosis and parakeratosis may be present on the tumor surface, and occasionally a prominent cutaneous horn may appear [3, 10, 25].

The histologic characteristic of IFK in our cases was a central inverted cup-shape configuration, similar to an opening of the pilosebaceous apparatus, confirming that these tumors can be closely related to the infundibulum of the hair follicle [11, 16]. Diagnosis was based on the observation of large lobules or finger-like projections of tumor cells exhibiting endophytic growth and extending into the dermis and composed of concentric layers of basaloid and squamous cells, with keratin toward the center and the presence of squamoid eddies [26]. Variable pigmentation, acantholysis, and mild inflammatory cell infiltrate, predominantly lymphohistiocytic, can be observed in the surrounding dermis [27].

The exact etiopathogenesis of IFK remains unknown. Some have postulated that the pathogenesis is related to viral warts [9, 11, 13], but the human papillomavirus has not been detected in most cases of IFK [12, 14]. Others believe that IFK could actually be an "irritated" seborrheic keratosis [15].

All our patients were treated with complete excisional biopsy with or without surgical closure techniques. This is the most common method of treatment [28]. Satisfactory results with topical 5% imiquimod cream were reported for 1 case [28]. No aggressive pattern was reported in our series, with only 1 exception of a recurrent lesion, which had a new surgical removal with a good outcome. A previous study reported recurrences in 2 cases weeks after an excisional biopsy technique [6].

In conclusion, IFK is uncommon in the periocular area. The lesion has no specific clinical characteristic, making

Table 2 Previous literature reports of periocular inverted follicular keratosis

Author, year [reference]	No. of cases described	Location	Age, y	Sex	Clinical diagnosis	Type of surgery	Recurrence
Boniuk et al, 1963 [16]	18	Upper eyelid (7) Lower eyelid (8) Not stated (3)	50 (median)	Not specified	Squamous cell carcinoma	Not specified	Not specified
Mehregan, 1964 [11]	2	Eyelid (1) Eyebrow (1)	50 (median)	Not specified	Not specified	Excisional biopsy	Not specified
Sim-Davis et al, 1976 [18]	4	Periorbital	Not specified	Not specified	Not specified	Not specified	Not specified
Scheie et al, 1977 [20]	1	Lower eyelid	70	Male	Cutaneous horn	Excisional biopsy	No
Sassani et al, 1979 [17]	17	Upper and lower eyelids	69 (median)	Not specified	Verruca (4) Papilloma (4) Skin lesion (3) Cutaneous horn (2) Granuloma (1) Senile keratosis (1) Carcinoma (1) Melanoma (1)	Excisional biopsy	No
Spielvogel et al, 1983 [29]	5 4	Upper eyelid Lower eyelid	Not specified	Not specified	Not specified	Not specified	Not specified
Schweitzer et al, 1987 [6]	2	Lower eyelid Eyebrow	61 73	Male Male	Wart "Growth"	Excisional biopsy Excisional biopsy	Yes Yes
Doxanas et al, 1987 [7]	1	Not specified	Not specified	Not specified	Squamous cell carcinoma	Excisional biopsy	Not specified
Mencia-Gutiérrez et al, 2002 [8]	1	Not specified	44.5	Not specified	Wart	Excisional biopsy	No
Ruhoy et al, 2004 [9]	1 (Cowden syndrome)	Right eyelid	50	Female	Not specified	Excisional biopsy	Not specified
Pointdujour-Lim et al, 2017 [10]	2	Upper eyelid Lower eyelid	54 (median)	Male	Cutaneous horn	Excisional biopsy	No

histopathologic confirmation imperative for correct diagnosis and treatment.

Conflicts of interest C. D.-Montero, None; D. G. González, None; E. P. Martinez, None; S. Schellini, None; A. G.-Ferreiro, None.

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