CASE REPORT

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Keratoacanthoma of the conjunctiva – case report and review of the literature

BIANCA AURORA SZABO[1)], ALINA SIMONA ŞOVREA[2)], DANA MONICA BARTOŞ[1)], ADRIAN BARTOŞ[3)], CARMEN GEORGIU[4,5)]

[1)]*Discipline of Anatomy and Embryology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[2)]*Discipline of Histology, Department of Morphological Sciences, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[3)]*Department of Surgery, "Prof. Dr. Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania*

[4)]*Discipline of Pathology, Department of Morphological Sciences, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[5)]*Department of Pathology, Emergency County Hospital, Cluj-Napoca, Romania*

Abstract

Introduction: Keratoacanthoma (KA) is a relatively common, benign, rapidly growing and self-limiting squamous proliferation, which appears most frequently on the sun-exposed skin. The nature of KA and its relationship to squamous cell carcinoma (SCC) still represent one of the major debates in dermatopathology, as it is the truthfulness of such a diagnosis outside the skin. However, the tumor is now known to originate from the pilosebaceous units of the skin or from ectopic sebaceous glands of squamous mucous membranes, and to differentiate onto follicular isthmus/infundibulum-like epithelium. *Case presentation*: A 71-year-old man presented with a sore and red right eye, which on slit-lamp biomicroscopical examination revealed a dome-shaped lesion at the temporal inferior conjunctival limbus. After a thorough histopathological examination, a diagnosis of KA has been made, both after the initial tumor excision and after the relatively rapid recurrence. After the second intervention, no recurrence was observed over five years of follow-up, confirming the diagnosis. *Conclusions*: The peculiarity of the case stands in his exceptional rarity, being to our knowledge the first conjunctival KA reported in our country. In the light of current knowledge, the peculiar limbal location of all the conjunctival KAs reported in the literature raised the question of the possible role of limbal stem cells in the histogenesis of these tumors, similar to the pilosebaceous ones. The treatment of conjunctival KA remains the complete excision of the tumor, as it allows histopathological evaluation of the entire tumor and the exclusion of a KA-like SCCs or KAs with SCC component.

Keywords: keratoacanthoma, conjunctiva, limbal stem cells, pilosebaceous unit.

Introduction

Keratoacanthoma (KA) is a relatively common, benign, rapidly growing and self-limiting squamous proliferation, with distinctive diagnostic clinical features and histological criteria, but also with many similarities with well-differentiated squamous cell carcinoma (SCC) [1–3]. In many cases, the differential diagnosis is very difficult, and because of the unpredictable malignant behavior of rare cases of KA, this tumor is still considered and coded as borderline tumor by *International Statistical Classification of Diseases* (ICD-O code 9071/1) [1]. However, this consideration is more appropriate because SCC occur about three times more often than KA [3, 4].

KA has a peak incidence between the sixth and seventh decades of life, with male preponderance [1, 5]. It is usually solitary, and arises in 95% of cases on the sun-exposed skin, especially on the face and dorsum of the superior extremities [4, 6]. Extra-dermatological sites have also been very rarely reported, meaning the squamous mucosa of the conjunctiva, tongue, oral mucosa, lip, pharynx, larynx, external genitalia and anal canal [1, 3, 6]. Many variants of KA have been recognized: solitary, giant, agglomerate and multi-nodular (*centrifugum marginatum*) subtypes, all involving mainly the skin, subungual KA and the extremely rare syndromic subtypes (Ferguson–Smith, Grzybowski's, Witten–Zak, and Muir–Torre syndromes), which manifest with large numbers of KAs on the skin and on the mucosa [2–4].

The etiology of KA is not well known. The most important etiological factor is the chronic irritation of the skin, especially the actinic damage, but it was also related to trauma, burns, tar exposure, human papillomavirus (HPV), immunosuppression and genetic factors [3, 4, 7].

Although KAs are very frequent on the face (70%), explained by the frequent sun-exposure of the facial skin, the periocular involvement (lower or upper eyelid, and medial or lateral canthus) is surprisingly uncommon (5.6% in one large series), the conjunctival location being even rarer, those described in the literature being just isolated case reports [7–15]. However, the location of some documented cases on the bulbar conjunctiva within the palpebral aperture, highlight the sunlight as etiology, as is the finding of solar elastosis [11].

This report presents a very rare case, of a rapidly growing conjunctival limbic mass diagnosed as conjunctival KA, with some analogies with other dermatological or

mucosal KAs, especially regarding the differential diagnosis and histogenesis of the tumor.

Case presentation

In 2011, a 71-year-old man was admitted at the Emergency Ophthalmologic Department, Cluj-Napoca, Romania, for a sore and red right eye. The patient presented hyperemia of the right bulbar conjunctiva associated with a foreign body sensation, of few weeks, duration. There was no history of trauma or previous ophthalmic surgery. All routine investigations were within normal range.

Slit-lamp biomicroscopy of the right eye revealed a white, dome-shaped mass at the temporal and slightly inferior limbus of the bulbar conjunctiva, surrounded by moderate conjunctival hyperemia. The mass was 8/6/4 mm in size, and cup-shaped, with a central crater filled with white material (Figure 1a). The tumor was apparently mobile and it was surrounded by dilated episcleral vessels. There were no enlarged lymph nodes. Other ophthalmic examinations were normal. Radiological investigations excluded intraocular radiopaque foreign material. At this point, the clinical features raised several differential diagnosis including conjunctival granuloma, inflamed pinguecula and conjunctival SCC.

The conjunctival lesion was excised, with retro-bulbar anesthesia. It was partially adherent to the underlying sclera and cornea, at the level of the sclero-corneal limbus. The excised specimen, placed immediately in 9% formalin, was processed for conventional Hematoxylin and Eosin (HE) histological examination.

Two months later, a 2/1/1 mm recurrence of the tumor was observed. The biomicroscopy of the eye revealed a protruding lesion with a central keratin deposit on the site of the previous tumor (Figure 1b). The lesion was excised with peribulbar anesthesia. Topical fluorometholone was prescribed for the immediate post-surgery period, which was without complications. Weekly follow-ups were scheduled. At 12 months after excision, the patient did not reveal any other recurrence of the lesion (Figure 1c).

The histological examination of both specimens demonstrated a hyperkeratotic squamous proliferation (Figure 2, a and b). The epithelium was acanthotic and endophytic, with well-delimited lobules extending downwards and slightly overhanging epithelial lips (Figure 2b). The squamous cells had abundant, pale, glassy eosinophilic cytoplasm and low nuclear pleomorphism (Figure 2, c and d). A moderate number of keratinous pearls was present throughout the lesion. The mitotic activity was low and mainly in the basal layers. At the periphery of the lesion, there was higher basal nuclear atypia and crowding (Figure 2e). There were no signs of stromal invasion. The stroma presented a moderate lymphocytic infiltrate and a reduced number of neutrophils with focal intraepithelial extension (Figure 2d). Normal conjunctival epithelium was observed at the slightly overhanging resected edges (Figure 2, a, c and d).

A diagnosis of conjunctival KA was made, excluding a SCC.

No recurrence was observed over five years of follow-up.

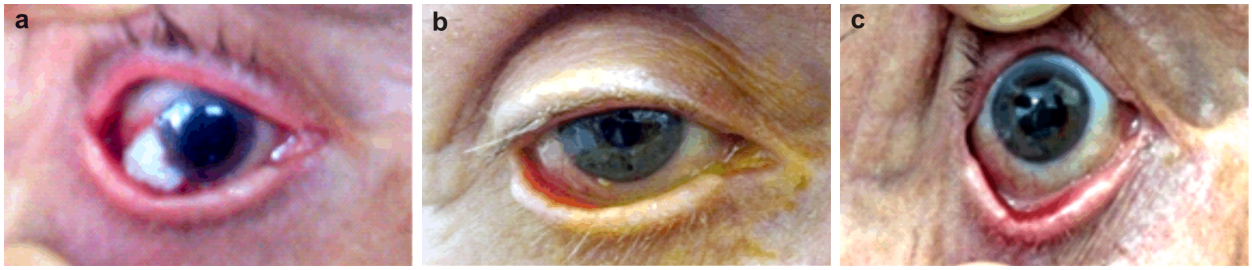

Figure 1 – ***Patient's right eye: (a) At admission, with a small white elevated tumor of the temporal and inferior bulbar conjunctiva, moderate chemosis and irritation and redness of the conjunctiva; (b) After the tumor recurrence, with a very small protruding lesion on the site of the previous tumor; (c) One year after surgery, with normal aspect of the anterior segment of the eye.***

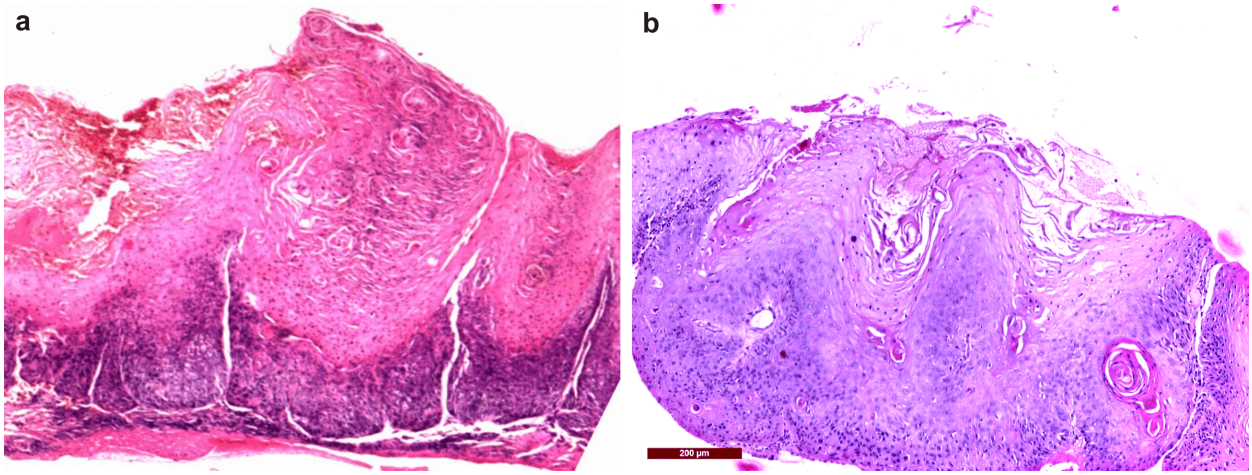

Figure 2 – ***Microscopic features of the conjunctival keratoacanthoma in HE staining (×100): (a) The primary tumor and (b) the recurrence, both with multi-lobular hyperkeratotic lesion with acanthotic squamous epithelium.***

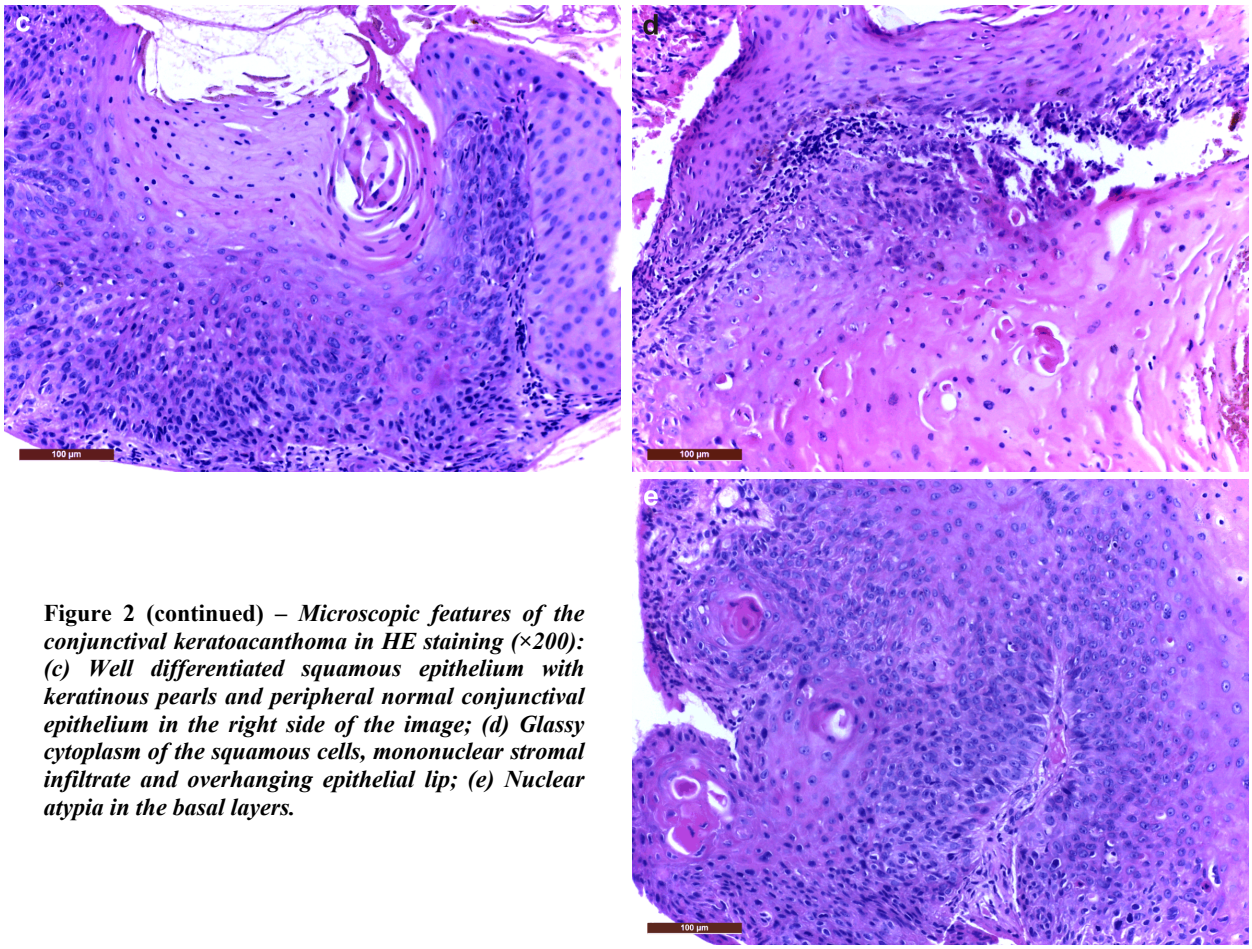

Figure 2 (continued) – ***Microscopic features of the conjunctival keratoacanthoma in HE staining (×200): (c) Well differentiated squamous epithelium with keratinous pearls and peripheral normal conjunctival epithelium in the right side of the image; (d) Glassy cytoplasm of the squamous cells, mononuclear stromal infiltrate and overhanging epithelial lip; (e) Nuclear atypia in the basal layers.***

Discussion

The nature of KA and its relationship to SCC represent one of the major debates in dermatopathology [16], as it is the truthfulness of such a diagnosis outside the skin. Moreover, it is considered by some authors a perfectly benign tumor, by others a borderline tumor, and by others a variant of very well differentiated SCC. However, the overdiagnosis of a lesion as SCC can have as serious consequences for the patient as an underdiagnosis as KA [4].

In dermatology, the most important features of these tumors are considered to be the rapid enlargement and the spontaneous regression of a flesh colored crater-like nodule with a central keratotic plug [17, 18]. These features were also described at the present case, with the exception of the spontaneous regression, the tumor being surgically treated and presenting a rapid recurrence, most probably because of an incomplete initial excision. The histological feature, that of a classic crater with a keratotic plug was also less visible, the tumor being in an intermediary, early to well-developed stage, and histologically creating difficulties in the differential diagnosis with other KA-like lesions, which are more frequently found on the conjunctival mucosa.

Recently, Misago *et al.*, in a series of researches, highlighted on the skin the various KA simulants [17–22]. They tried also to clarify how these lesions behave after partial biopsy, the regression being a characteristic of KA, but paradoxically appearing in rare cases of KAs with malignant SCC component [23, 24]. However, Ra *et al.*, using DNA microarrays, proved that KA and SCC are different from a molecular perspective, with more than thousand differentially expressed genes in comparison with SCC. Comparing with normal skin, they also suggested that KA is a neoplasm that can regress due to up-regulation of the cell death/apoptosis pathway [25, 26]. Despite of the molecular differences between KA and SCC, the rare and unpredictable malignant transformation of KA is however a reality, in some cases being described a component of regressing KA in continuity with a frankly malignant squamous component [18].

Regarding the differential diagnosis with KA simulants, the pathological changes in the early proliferative stage of a KA must be differentiated from the well-differentiated infundibulocystic SCC reported by Kossard *et al.* [16, 18]. The well-developed crateriform stage must be differentiated from a KA with SCC components (KA with malignant transformation and, respectively, KA-like SCC), their confusion being the worse misdiagnosis [17, 18, 22]. There are also other types of crateriform epithelial tumors, more or less ominous, appearing mostly but not exclusively on the skin, which should be distinguished from KA: crateriform SCC arising from solar keratosis, crateriform (pigmented) Bowen's disease, crateriform seborrheic keratosis, crateriform verruca [17, 18, 22]. The same, Misago *et al.* recently clarified, both morphologically and immunohistochemically [by complete loss of the cytokeratin (CK) 15 hair stem cell marker], the follicular differentiation, toward infundibulum and/or isthmus, of skin KA. This differentiation depends on the pathological stage of the tumor: infundibular for the early stage,

isthmic for the well developed and epidermal for the regressed stage [27, 28]. It means also that the association of solar keratosis or Bowen's disease excludes the diagnosis of KA of the skin, being of epidermal origin.

Because a large number of evidence supports the origin of KA in pilosebaceous follicle, some authors deny the existence of conjunctival KA or other mucosal KAs [2]. However, there are cases reported in areas such as oral mucosa, vermilion, limbal conjunctiva and other sites, where ectopic sebaceous glands may be found [2]. In addition, the infundibulum and isthmus are the superficial part of the pilosebaceous unit, superior to the sebaceous gland, thought to contain preprogrammed progenitor cells, possible source for KA [2]. In fact, in the hair follicles, a compartment of multipotent stem cells is located in the bulge, which lies just below the sebaceous gland. These cells contribute by transiently amplifying progeny to the lineages of the hair follicle, sebaceous gland, and the epidermis [29], and arriving in the isthmus and the infundibulum may be the most probable origin of KA. In fact, some of the extra tegumentary KAs are located in or near the transition sites between slightly two different epithelia (limbal conjunctiva, distal subungual, muco-cutaneous lines) [2, 3, 7, 30], which may contain multi-potent stem cell niches, similar to the pilosebaceous unit.

Within the limbal region of the conjunctiva, a stem cell niche similar to the pilosebaceous bulge is already described. Limbal multipotent epithelial stem cells are proved to be located in the basal layer of the undulating epithelium and have the ability to regenerate the entire corneal epithelium. They produce daughter transient amplifying cells, which divide and migrate towards the central cornea to replenish the epithelium with terminally differentiated epithelial cells. Limbal stem cells also prevent the conjunctival epithelial cells from migrating onto the epithelium of the cornea [31, 32]. Regarding conjunctival KA, the typical location of the tumor is the limbic region, mainly temporal (as in the present case), but also in the nasal part of the limbus, corresponding to the palpebral aperture [7, 10]. This specific location point to the multipotent limbal epithelial stem cells as possible source of KA, and to sunlight as etiological factor. Other peculiar tumors reported in the limbic region of conjunctiva are strongly related, as for example a sebaceous gland carcinoma (origin in ectopic sebaceous glands) and dermoid tumors (considered choristomas, and containing skin elements, including pilosebaceous units) of the conjunctiva [33–35]. However, the multi-potent limbal stem cells may also be considered as potential source for all these aberrant tumoral or choristomatous differentiations.

Other KAs may have similar origins. For example, subungual KA may be related to the multipotential stem cells of the nail. These cells, located in the nail matrix (nail plate actively proliferating matrix or in the nail bed matrix), similarly to the follicular bulge may contribute by transiently amplifying progeny to the lineages of the nail plate, but also of the epidermis via the nail bed and the hyponychium [36]. In this aspect, the hyponichium appears to be very similar to the isthmic/infundibular portion of the hair. Sustaining this similarity, subungual KA appears more frequently in the distal part of the nail near hyponichia, and rarely in the proximal part [3].

Returning to limbal conjunctival KA, this neoplasm remains a rare disease, the present case being to our knowledge the first reported in our country. It must be considered as his dermatological counterpart a borderline tumor, with possible malignant transformation requiring ocular enucleation [7]. The capacity of spontaneous regression may be possible but not proved, and so, the "wait-and-see" management is not appropriate in this location, the best treatment being the complete excisional surgery, using no touch technique, cryotherapy and amniotic membrane [9]. The complete removal is essential, only the histopathological examination of the whole lesion leading to a correct diagnosis. This is a good example for the heterogeneity of a tumor on histological slides, each part of the crateriform nodule presenting a different histological image, each essential for the definitive diagnosis of an early, fully developed or regressing KA, or most importantly of KA with SCC components. Although the precise histogenesis of KA is unknown, the limbal conjunctival KA, as are the other mucosal KAs, appear to be the result of chronic irritation of transition zones between two slightly different squamous epithelia, which need multipotent stem cells for their turnover.

Conclusions

The peculiarity of the case stands in his exceptional rarity, being to our knowledge the first case reported in our country. KA is a relatively common, benign, rapidly growing and self-limiting squamous proliferation of the skin, which occasionally appears on mucous squamous membranes. It is known to originate from pilosebaceous units of the skin or ectopic sebaceous glands of squamous mucosa, and to differentiate onto follicular isthmus/ infundibulum-like epithelium. This report tried to connect the notions so far known about the limbal conjunctiva and his role in the corneal epithelium turnover with the preferential development of the conjunctival KA in the limbal region. There were also highlighted the similarities with the other mucosal KAs, especially regarding the differential diagnosis and the histogenesis of these tumors. The mainstay in the treatment of conjunctival KA remains complete excision, as it allows histopathological evaluation of the entire tumor and a correct diagnosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Consent

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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Corresponding author
Alina Simona Şovrea, Associate Professor, MD, PhD, Discipline of Histology, Department of Morphological Sciences, "Iuliu Haţieganu" University of Medicine and Pharmacy, 6 Pasteur Street, 400349 Cluj-Napoca, Romania; Phone +40744–786 688, e-mail: a_sovrea@yahoo.com

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