UNIVERSITE DE LAUSANNE – FACULTE DE BIOLOGIE ET DE MEDECINE

Hôpital ophtalmologique Jules Gonin

Service d'ophtalmologie

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Tumors of the Caruncle: A Clinicopathologic Correlation

THESE

présentée à la Faculté de biologie et de médecine de

l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Lausanne

2007

TUMEURS DE LA CARONCULE : CORRELATION CLINICO-PATHOLOGIQUE

BUT

Préciser le type et l'incidence des lésions de la caroncule. Investiguer la corrélation entre les diagnostics cliniques et histologiques.

METHODES

Nous avons revu les dossiers des patients ayant subi l'excision d'une lésion de la caroncule, soumis au département de pathologie oculaire de l'Hôpital Ophtalmique Jules Gonin entre janvier 1979 et mai 2005. Nous avons catalogué les lésions en fonction de leur type histologique. Nous les avons corrélées à l'âge et au sexe des patients, ainsi qu'au diagnostic clinique pré-opératoire.

RESULTATS

Nous avons identifié 195 lésions consécutives de la caroncule, provenant de 191 patients. Vingt-quatre types histologiques ont été répertoriés. Les lésions les plus fréquentes étaient les naevi (n = 92, 47%) et les papillomes (n = 29, 15%). Nous avons identifié un kérato-acanthome. Cent-huitante-trois (93.8%) lésions étaient bénignes, six (3.1%) étaient pré-malignes, et cinq (2.6%) étaient malignes. Le diagnostic clinique pré-opératoire correspondait au diagnostic histologique dans 73 (37.4%) cas. L'excision des lésions était fréquemment motivée par une suspicion de malignité (61 cas, 31.3%), qui n'a été confirmée que dans trois des 61 cas (4.9%). Deux des cinq pathologies malignes avaient un diagnostic clinique bénin.

CONCLUSIONS

Nous rapportons ici le premier cas de kérato-acanthome de la caroncule. La rareté et la variété des lésions caronculaires rendent leur diagnostic clinique difficile. La malignité est surestimée par l'appréciation clinique, alors que les lésions malignes peuvent avoir un aspect clinique bénin. Ceci justifie un suivi photographique régulier de toutes les lésions. Les lésions pigmentées nécessitent un suivi particulièrement attentif en raison du pronostic défavorable des mélanomes malins de la caroncule. En l'absence de critères de malignité bien établis, une lésion de la caroncule doit être excisée lors de tout changement de couleur, de taille ou de vascularisation.

Tumors of the Caruncle: A Clinicopathologic Correlation

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• PURPOSE: To determine the types and incidence of caruncular lesions and to investigate the correlation between clinical and histologic diagnosis.
• DESIGN: Retrospective, observational case series.
• METHODS: Records of patients with a lesion of the caruncle that was excised and submitted to our ocular pathology department between January 1979 and May 2005 were reviewed. Lesions were classified by histologic type and correlated with patient age, gender, and preoperative clinical diagnosis.
• RESULTS: A total of 195 consecutive caruncular lesions from 191 patients were identified. Twenty-four different types of lesions were identified; the most common were nevi (n = 92, 47%) and papillomas (n = 29, 15%). One keratoacanthoma was identified. One hundred eighty-three lesions (93.8%) were benign, six (3.1%) were premalignant, and five (2.6%) were malignant. Preoperative clinical diagnosis corresponded to postexcision histologic diagnosis in 73 cases (37.4%). Suspected malignancy was a common reason for excision (61 cases, 31.3%), but malignancy was confirmed in only three (4.9%) of 61 cases. Two of the five malignant lesions were clinically thought to be benign.
• CONCLUSIONS: We hereby report the first caruncular keratoacanthoma. The rarity and variety of caruncular lesions make clinical diagnosis difficult. Malignancy is clinically overestimated, and some malignant lesions can take a benign aspect, justifying close photographic follow-up of all lesions. Because caruncular malignant melanoma is associated with poor prognosis, pigmented lesions should be monitored carefully. In the absence of clear criteria for malignancy, any change in color, size, or vascularization of a caruncular lesion should hasten excision. (Am J Ophthalmol 2006;142:448–455. © 2006 by Elsevier Inc. All rights reserved.)

Accepted for publication Apr 11, 2006.

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Presented in part at the 23rd Congress of the European Society of Ophthalmic Plastic and Reconstructive Surgery, Sep 17, 2005, Island of Crete, Greece.

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THE CARUNCLE IS A NODULAR STRUCTURE LYING AT the internal canthus, medial to the plica semilunaris. The caruncle is widely exposed in the palpebral aperture, such that patients or physicians easily notice changes in its appearance. However, the rarity and variety of lesions that arise within the caruncle make their clinical diagnosis difficult.

von Graefe reported the first series of lesions of the caruncle in 1854.[1] Ash (1950), Luthra and associates (1978), Shields and associates (1986), Santos and Gomez-Leal (1994), and Hirsch and associates (1997) subsequently reported large series, illustrating the variety of caruncular lesions.[2–6]

To more precisely define both the nature and the incidence of caruncular lesions, we conducted a retrospective study of such lesions that were excised and submitted to our ocular pathology unit over a 26-year period.

METHODS

WE REVIEWED THE RECORDS OF 18,000 SPECIMENS SUBMITted to the ocular pathology unit of the Jules Gonin Eye Hospital, Lausanne, Switzerland, between January 1979 and May 2005. These specimens were submitted by ophthalmologists working at the Jules Gonin Eye Hospital or by physicians in private practice in western Switzerland. Initially, reports on all lesions involving the caruncle were reviewed, but this study describes only primary lesions of the caruncle. Lesions of the adjacent plica semilunaris and conjunctiva were excluded. Histologic slides were reviewed only when the diagnosis or the primary localization was in question. Clinical preoperative diagnoses were obtained by reviewing the histopathologic examination form submitted with the specimen or the clinical charts of patients who underwent surgery at our institution. This study was performed in accordance with the tenets of the Declaration of Helsinki.

RESULTS

ONE HUNDRED NINETY-ONE PATIENTS WERE INCLUDED IN the study. There was an equal distribution of men (n = 94)

0002-9394/06/$32.00
doi:10.1016/j.ajo.2006.04.035

TABLE. Classification of Lesions of the Caruncle

Pathologic Diagnosis	n	%	Age (mean/median, y)	Age (range, y)	Male	Female
Melanocytic tumor						
Nevus	92	47.18	44/43	5–87	41	51
Dysplastic nevus	2	1.03	69	56–82	1	1
Primary acquired melanocytosis	1	0.51	59	—	—	1
Malignant melanoma	1	0.51	54	—	—	1
Benign epithelial tumor						
Papilloma	29	14.87	47/48	21–70	21	8
Sebaceous gland hyperplasia	15	7.69	57/53	32–78	10	5
Sebaceous gland adenoma	2	1.03	62.5	59–66	1	1
Epidermoid cyst	10	5.13	44/43.5	13–67	6	4
Oncocytoma	7	3.59	72/73	49–87	—	7
Sweat gland cyst	1	0.51	42	—	1	—
Pilar cyst	1	0.51	43	—	—	1
Keratoacanthoma	1	0.51	44	—	—	1
Premalignant epithelial tumor						
Carcinoma in situ	2	1.03	41.5	35–48	—	2
Dysplasia within papilloma	1	0.51	53	—	1	—
Malignant epithelial tumor						
Primary basal cell carcinoma	2	1.03	62.5	53–72	1	1
Sebaceous gland carcinoma	1	0.51	60	—	—	1
Inflammatory lesions	13	6.67	62/69	33–80	7	6
Nonspecific changes						
Fatty infiltration of unknown origin	2	1.03	66.5	51–82	—	2
Elastoid degenerative changes	1	0.51	52	—	1	—
Edema	2	1.03	51.5	49–54	1	1
Inflammatory tumorlike lesion (Pyogenic granuloma)	3	1.54	49/49	48–50	1	2
Mesenchymal/vascular tumor						
Cavernous hemangioma	1	0.51	50	—	1	—
Capillary hemangioma	2	1.03	35	28–42	1	1
Normal tissue	2	1.03	57.5	57–58	2	—
Lymphoid tissue tumor (isolated low-grade malignant lymphoma)	1	0.51	48	—	1	—

and women (n = 97) (ratio 1:1.03). Patients underwent lesion excision at a mean age of 48.5 years (range five to 87 years). We identified a total of 195 consecutive lesions of the caruncle. This represents an incidence of 1.1% (195 of 18,000) of all specimens submitted to the ocular pathology unit. Sixty-five lesions (33%) were submitted by ophthalmologists working at the Jules Gonin Eye Hospital and 130 lesions (67%) by ophthalmologists in private practice. Lesion classifications by type, patient age, and gender are listed in the Table.

The most commonly observed lesions (n = 96) were melanocytic tumors. Of these, nevi were most common, representing 96% (92 of 96) of melanocytic tumors (Table). Nevi clinically appeared as brown pigmented lesions, although the size and color were highly variable (Figure 1). The mean patient age at nevi excision was 44 years (range five to 87 years). We noted a slight female predominance, with nevi occurring in 51 women and 41 men. Histologically, the nevi were composed of epithelial and/or subepithelial nests of benign melanocytic cells; mitosis, nuclear atypia, and pleomorphism were not present.

Two types of lesions in the melanocytic tumor group were classified as premalignant conditions: dysplastic nevi (n = 2) and primary acquired melanocytosis (n = 1). Only one malignant melanoma was collected during the more than 26 consecutive years of the study. The melanoma was excised from a 54-year-old woman who noticed a growth at the internal canthus three weeks before consultation. A pigmented caruncular lesion was noted at examination and was excised because malignancy was suspected. Histologic examination revealed small clusters of atypical epithelioid melanoma cells in the conjunctival epithelium and stroma (Figure 2). The excision was complete, and no additional therapy was provided. There was no local recurrence and no evidence of metastases or systemic involvement during 23 years of follow-up.

Epithelial tumors accounted for 37% (72 of 195) of all caruncular lesions (Table). Ninety-two percent (66/72) were benign. Papilloma was the most common type of epithelial tumor (29 lesions). The mean age at excision was 47 years (range 21 to 70 years), and men (n = 21) were more commonly affected than women (n = 8); the

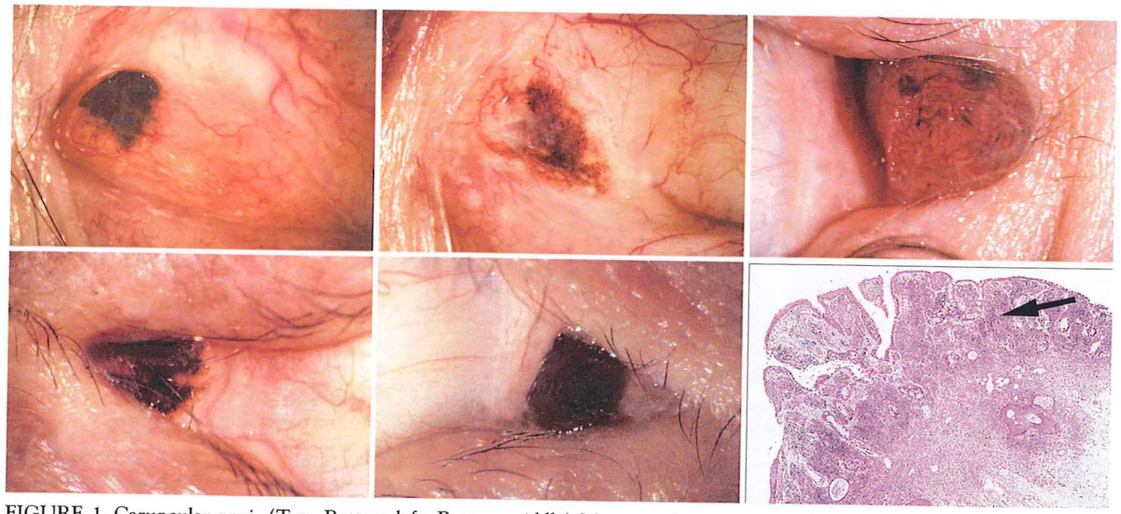

FIGURE 1. Caruncular nevi. (Top, Bottom left, Bottom middle) Macroscopic appearance of nevi shows variations in size and pigmentation. (Bottom right) Histology shows subepithelial nests of benign melanocytic cells (arrow) (hematoxylin and eosin; original magnification, ×40).

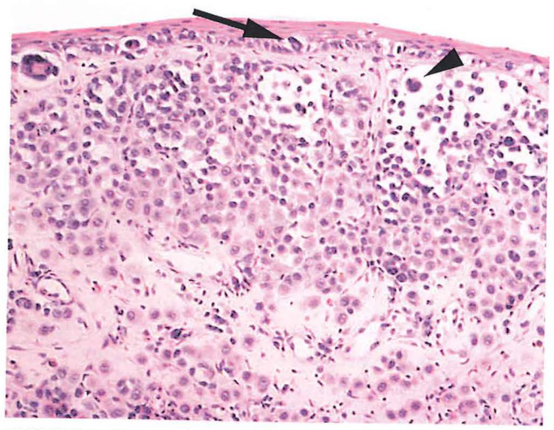

FIGURE 2. Caruncular malignant melanoma. Histology shows atypical epithelioid melanoma cells in conjunctival epithelium (arrow) and stroma (arrowhead) (hematoxylin and eosin; original magnification, ×200).

male-female ratio was 2.75:1. Clinical examination revealed that papillomas showed the typical cauliflower-like appearance. Histologically, the tumors were composed of fibrovascular fronds covered by acanthotic conjunctival epithelium (Figure 3).

The second most commonly observed epithelial lesion was sebaceous gland hyperplasia (Table). Clinically it appeared as a greasy, granular, yellowish tumor. Histology revealed mature sebaceous lobules grouped around a central duct (Figure 4). Additional benign epithelial tumors included epidermoid cysts (n = 10), oncocytomas (n = 7), sebaceous gland adenomas (n = 2), sweat gland cyst (n = 1), and pilar cyst (n = 1).

One tumor was reported to have grown in three days, before being excised because of suspected malignancy. Histologic examination of the excised lesion revealed an incipient central crater with overhanging edges of squamous epithelium surrounded by an acanthotic epithelium, and with an intact basal cell layer (Figure 5). Accordingly, a diagnosis of keratoacanthoma was made. No recurrence was noted after excision.

Three epithelial tumors were classified as premalignant lesions. Two of these were carcinomas in situ, and one was a papilloma with marked dysplasia.

There were three malignant epithelial tumors, two of which were primary basal cell carcinomas. One of these primary basal cell carcinomas occurred in a 72-year-old woman who presented with a recently noted caruncular lesion that at examination was clinically diagnosed as an epithelial cyst. The second primary basal cell carcinoma occurred in a 52-year-old man who noted a rapidly growing pigmented caruncular lesion. Clinically, this tumor was thought to be a malignant melanoma (Figure 6), but histologic examination revealed an unusual macronodular, pigmented basal cell carcinoma. The tumor contained both pigmented dendritic melanocytes and rounded melanophages, and macronodules with peripheral palisading, surrounded by retraction cleft, were present. In toto excision was curative in both cases, and no recurrence was noted at the end of the follow-up period. The third malignant epithelial tumor was a sebaceous gland carcinoma occurring in a 60-year-old woman who presented with nonpigmented enlargement of the caruncle. This

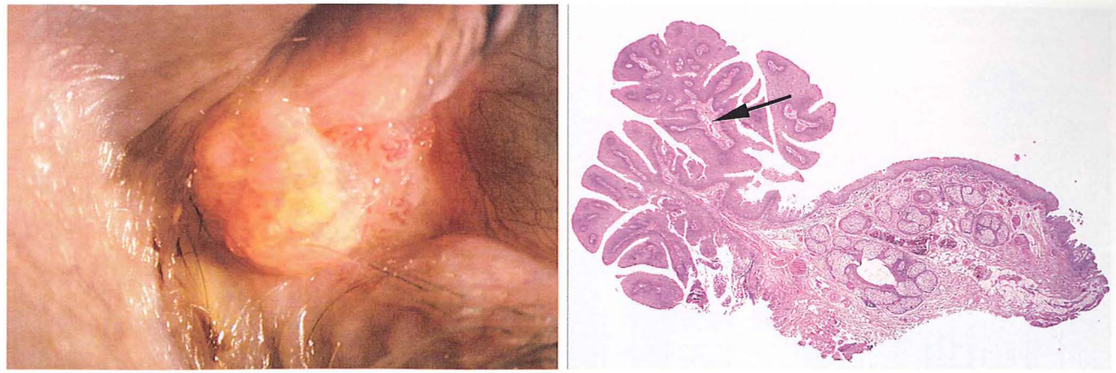

FIGURE 3. Caruncular papilloma. (Left) Macroscopic "cauliflower" aspect of papilloma. (Right) On histology, tumor is composed of fibrovascular fronds (arrow) covered by acanthotic conjunctival epithelium (hematoxylin and eosin; original magnification, ×20).

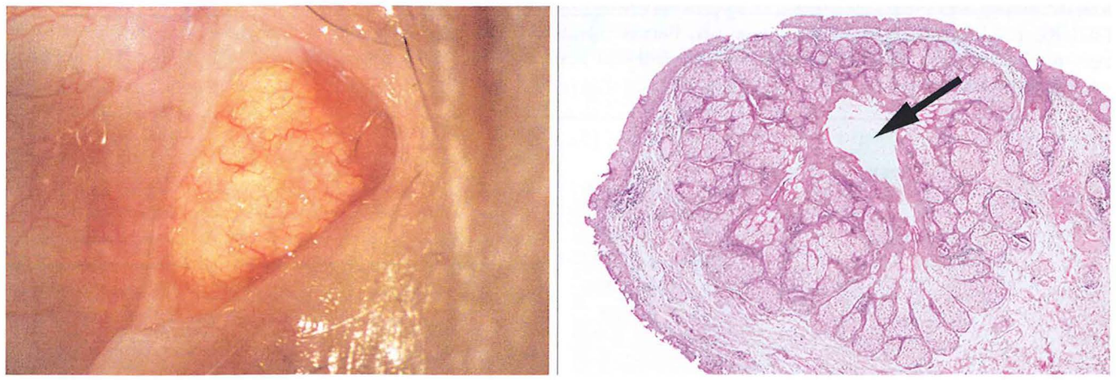

FIGURE 4. Caruncular sebaceous gland hyperplasia. (Left) Clinical appearance of sebaceous gland hyperplasia is greasy, granular, yellowish tumor. (Right) Histology shows mature sebaceous lobules grouped around central duct (arrow) (hematoxylin and eosin; original magnification, ×40).

lesion was clinically thought to be benign. Excision was curative. Neither local recurrence nor metastasis was noted over 17 years of follow-up.

Inflammatory lesions, nonspecific changes, and inflammatory tumorlike lesions together accounted for 11% (21 of 195) of all caruncular lesions identified (Table). Vascular tumors included two capillary hemangiomas and one cavernous hemangioma.

One lesion was classified as a lymphoid tissue tumor. It arose in a 48-year-old man who presented with a lesion that had been slowly growing for two years. This lesion was suspected to be malignant and was therefore widely excised. The pathologic morphologic examination resulted in a differential diagnosis of low-grade mucosa-associated lymphoid tissue (MALT) lymphoma vs reactive lymphoid hyperplasia. However, polymerase chain reaction showed a monoclonal rearrangement band, thereby confirming the diagnosis of low-grade MALT lymphoma. Thoracoabdominal computerized tomographic scan and a medullary biopsy were performed but revealed no additional lesions. The caruncular lymphoma was thus considered to be an isolated occurrence. A six-year follow-up showed no evidence of local or systemic lymphoma. Histologic examination of two excised caruncles found nothing abnormal.

The preoperative clinical diagnosis was confirmed by histopathologic examination in 37.4% (73 of 195) of the cases. Although malignancy was suspected in 61 cases (31.3%), it was confirmed in only three. However, two (40%) of the five malignant lesions were clinically thought to be benign.

DISCUSSION

THE CARUNCLE IS COMPOSED OF ELEMENTS OF CONJUNCtival, cutaneous, and lacrimal origin. It is covered by stratified, nonkeratinized squamous epithelium and is associated with sebaceous glands, hair follicles, sweat glands,

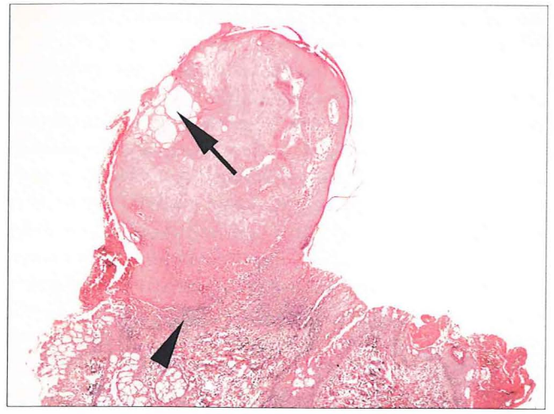

FIGURE 5. Histology of caruncular keratoacanthoma. An incipient crater is present (arrow) with overhanging edges of squamous epithelium surrounded by an acanthotic epithelium, with an intact basal cell layer (arrowhead) (hematoxylin and eosin; original magnification, ×40).

accessory lacrimal glands, and goblet cells. The caruncular body is formed by fatty and connective tissue and contains some muscle fibers associated with the medial rectus. There is a dense blood supply derived from the superior medial palpebral artery. Lymphatics drain to the submaxillary lymph nodes, and the caruncle is innervated by the infratrochlear nerve.[7] Although the function of the caruncle is not well understood, it may participate in lacrimal drainage by passively transmitting the contractions of the orbicularis muscle to the lumen of the canaliculi and the lacrimal sac.[8]

Caruncular lesions are rare, representing only 1.1% of all surgical specimens submitted to the ocular pathology unit of the Jules Gonin Eye Hospital during the 26 years of the study. This incidence is in agreement with the incidences previously reported (0.3% to 1.1%).[3–6] The 24 different lesion types that we identified illustrate the diversity of caruncular pathology, which can be accounted for by the diversity of the histologic components of the caruncle.

We report a keratoacanthoma arising in the caruncle, thus extending the differential diagnosis of caruncular lesions. We are unaware of previous reports of a keratoacanthoma of the caruncle and could find no reference to such an entity in a computerized search of the MEDLINE database. Keratoacanthoma occurs only rarely in the conjunctiva. The first case of conjunctival keratoacanthoma was reported by Freeman and associates in 1961,[9] and only 13 cases have been reported since that time.[10–20] Cutaneous keratoacanthoma typically shows rapid growth before undergoing spontaneous regression. The natural history of their conjunctival counterparts is unknown because of early excision. Histologic features of cutaneous keratoacanthoma include a keratin-filled central crater surrounded by an acanthotic epithelium with an intact basal cell layer.

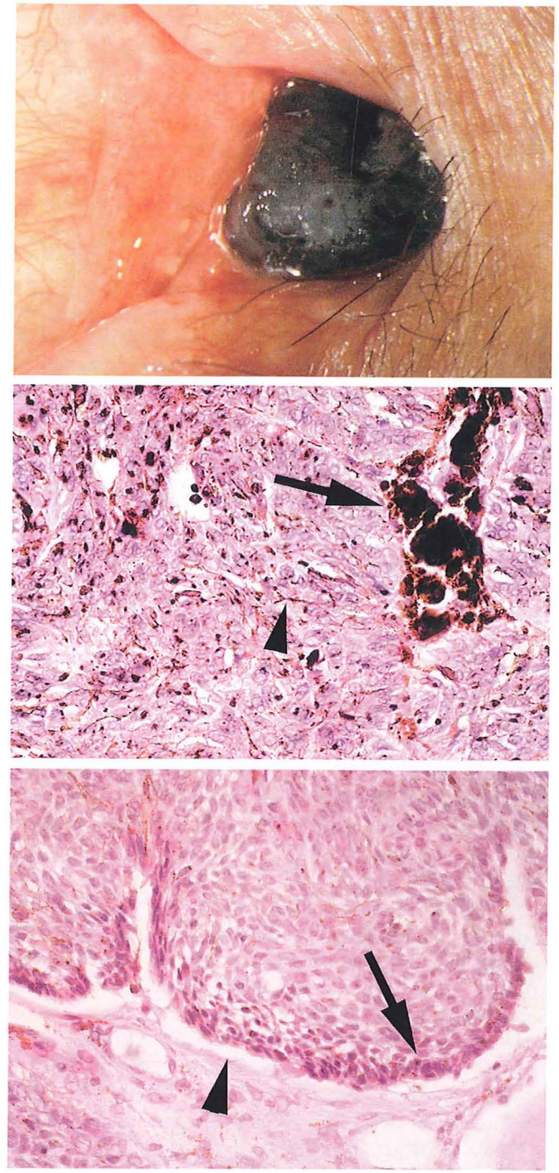

FIGURE 6. Caruncular basal cell carcinoma. (Top) Macroscopic appearance of macronodular pigmented basal cell carcinoma, apparent as darkly pigmented tumor. (Middle) Histologic examination found pigmented dendritic melanocytes (arrowhead) and rounded melanophages (arrow) inside and between carcinomatous lobules (hematoxylin and eosin; original magnification, ×400). (Bottom) Tumor nodule with typical peripheral palisade (arrow) and retraction cleft (arrowhead) (hematoxylin and eosin; original magnification, ×400).

However, the crater-like shape may be absent in conjunctival keratoacanthoma.[9,10,14] Keratoacanthoma is thought to originate from hair follicles[16] or ectopic sebaceous

glands.[21] The primary differential diagnosis of keratoacanthoma is well-differentiated squamous cell carcinoma, which characteristically develops more slowly (over months to years), is not well delineated, and generally has no central crater. In contrast to keratoacanthoma, histologic examination of squamous cell carcinoma shows epithelial dysplasia, pleomorphism, abnormal mitoses, desmoplastic stroma, and invasive features.[22] The treatment of keratoacanthoma is complete excision.

Differences in the methods of data collection in this and previous studies limit comparisons of the reported incidence of the various types of caruncular lesions. However, the two most frequently excised lesions in both the present study and previously published series are nevi and papillomas. Previous studies reported nevi as representing 25% to 45% of all lesions of the caruncle, with papilloma representing 13% to 37% of caruncular lesions.[2–6] In our series, nevi accounted for 47% (92 of 195) of the lesions, but their size, morphology, and pigmentation were highly variable. Size and pigmentation changes are not uncommon, typically occurring at puberty or during pregnancy, and with no evidence of malignant transformation. Shields and associates[23] reported a series of 410 patients with conjunctival nevi, of whom 176 (43%) reported a change in size or color of the lesion. One hundred forty-nine (36%) of these same 410 patients were observed over time, during which period further changes in color became evident in 19 of them (13%), and 12 (8%) experienced a change in nevus size.[23] Mechanisms for nevus growth include inflammation within the lesion, cystic enlargement, and increased pigmentation.[23–26] Risk of malignant transformation is low.[24,27,28] Shields and associates[23] reported transformation in only three (0.7%) of 418 conjunctival nevi, all of which occurred in nevi with a history of enlargement. Gerner and associates[29] reported one case of malignant transformation among the nine (of 341) nevi that recurred after excision. Nevus enlargement is thus more often attributable to inflammation or benign evolution than to malignant transformation. In contrast, 4% to 17% of malignant melanomas are reported to have developed in preexisting nevi.[25,30,31]

Two basal cell carcinomas were included in our series of lesions of the caruncle, one of which was an unusual macronodular, pigmented basal cell carcinoma. Basal cell carcinoma is the most frequent malignant lesion of the eyelid, accounting for 80% to 90% of eyelid cancers,[32] but it occurs very rarely on the conjunctiva or caruncle. To our knowledge, only six cases of basal cell carcinoma of the caruncle have been reported.[4,6,33–36] Caruncular localization of basal cell carcinomas could be explained by their origin from totipotential epithelial stem cells or the pilosebaceous structure.[32] Basal cell carcinomas rarely metastasize but have a potential for local invasion. They are the third most common invasive orbital malignancy and can cause death if they invade the central nervous system.[32,37] Recurrences of these tumors have been described even after complete excision, making long-term follow-up mandatory.[32]

Melanoma has been reported to be the most prevalent malignant lesion of the caruncle.[2–6] However, its occurrence on the caruncle is rare compared with its occurrence on the conjunctiva.[25,38–40] In our study, only one case of melanoma was identified. Caruncular melanoma corresponds to a T3 stage of the TNM classification of the International Union Against Cancer[41] and is thought to have a poor prognosis.[40,42] Reported treatments for caruncular or conjunctival melanoma include wide excision, adjuvant cryotherapy, and radiotherapy, or orbital exenteration for tumors with local extension.[3,43,44] The favorable outcome of our case might be explained by the fact that in toto excision with wide margins was performed.

We collected two additional malignant lesions in our series: one sebaceous gland carcinoma and one isolated low-grade malignant lymphoma. There are reports of squamous cell carcinoma[4,6] and Kaposi sarcoma[6] occurring within the caruncle. However, only one case of a metastatic lesion of the caruncle, from a large-cell neuroendocrine lung carcinoma, has been reported.[45]

In total, only 2.6% (five of 195) of all caruncular lesions in our study were malignant. This finding is consistent with the large series of Luthra and associates,[3] which reported a malignancy rate of 2.7%. Elsewhere, malignancy rates between 4.9% and 6.1% have been reported.[2,4–6] We could not find any element suggestive of a lower susceptibility to development of malignant lesions in the caruncle compared with other locations in the human body. Thus, we propose that the low malignancy rate of the caruncular tumors is related to the excessively frequent excision of benign lesions, which itself could be explained by the rarity of caruncular lesions, which are less familiar to clinicians. The rarity of the lesions also explains the lack of malignancy criteria. Knowing the poor prognosis related to caruncular malignant melanoma,[40,42] practitioners may often choose to remove any pigmented lesion. Furthermore, because of the prominent exposure of the caruncle in the palpebral aperture, any alteration in caruncular appearance is easily noticed by patients, who for cosmetic and psychological concerns may urge the surgeon to excise the lesion. Inflammatory and cystic enlargement represent a nonmalignant cause of lesion enlargement that also leads to precocious excision. In these situations, excision is motivated by suspicion of malignancy or functional impairment. The low rate of malignancy might also be explained by the small size of the caruncle.

In the series described herein, we found caruncular malignancies to have a good prognosis. In toto resection appeared to be curative in all five of the cases included here; no additional therapy was provided. Again, the exposed location of the caruncle, which allows both the patient and the ophthalmologist to note any early change, leads to early care, which may contribute to the favorable prognosis. Luthra and associates[3] reported cases of malignant caruncular tumors with local or systemic invasion that mandated more aggressive therapy and were associated with a worse outcome.

The preoperative clinical diagnosis was confirmed by histologic examination in 37.4% of all cases (73 of 195). This is a lower rate than in previously published studies, which reported 50.4% to 52.6% of clinical diagnoses to be correct.[4,5] Suspicion of malignancy was a common reason for excision (61 of 195 lesions, 31.3%), as was esthetic or functional impairment. There was a clear clinical overestimation of malignancy: only 4.9% (three of 61) of the suspect cases proved to be malignant. However, two of the five cases in our series that proved to be malignant had a benign clinical diagnosis: a sebaceous gland carcinoma was clinically diagnosed as caruncular hypertrophy, and a basal cell carcinoma had a preoperative diagnosis of epithelial cyst.

The poor correlation between clinical diagnosis and histologic diagnosis found in our series can be explained by the large pathologic variety of lesions encountered. Herein, for example, we have reported the first keratoacanthoma of the caruncle; we are unaware of previous description of such a lesion. Moreover, lesions such as nevi may have very different clinical appearances, making accurate clinical diagnosis even more difficult. Most of the lesions were diagnosed and excised by general ophthalmologists, working either within our institution or as private practitioners; the clinical evaluation was not made by an oncologist. Ophthalmologists often consider growth and/or change in pigmentation, as well as swelling and keratinization of a caruncular lesion, indications of malignancy. However, these changes are most often unrelated to malignancy, caused instead by inflammation or benign evolution. Because of the rarity of caruncular lesions, general ophthalmologists have little expertise with their diversity and growth mechanisms, precluding accurate clinical diagnosis.

In conclusion, the rarity and variety of caruncular lesions make clinical diagnosis difficult. There is a clear clinical overestimation of malignancy. Close photographic follow-up of all lesions is warranted because some malignant lesions have a benign aspect. Caruncular malignant melanoma is associated with poor prognosis, and pigmented lesions should therefore be monitored carefully. In the absence of clear criteria for malignancy, any change in color, size, or vascularization of a caruncular lesion should hasten excision.

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