A woman in her mid-50s was referred for evaluation of a diffuse left upper eyelid tumor with ptosis (Figure 1A). The mass had been noted 3 months earlier. There was blurry vision over 3 months. B, Eversion of the eyelid reveals diffuse palpebral conjunctival thickening caused by a faintly corrugated or papillary mass exhibiting a nonkeratinizing surface. This appearance is most characteristic of a squamous lesion, but occasionally sebaceous tumors may present as a papillary mass. C, In the top panel, infiltrating tumor displays the eosinophilic cytoplasm of an epidermoid (squamous) proliferation (hematoxylin-eosin, original magnification ×12.5); in the bottom panel, areas of necrosis (comedonecrosis [arrowheads]) superficially suggest a sebaceous carcinoma (hematoxylin-eosin, original magnification ×100). D, Higher-power photomicrograph shows comedonecrotic focus with surrounding viable eosinophilic cells occasionally displaying vacuoles (hematoxylin-eosin, original magnification ×400). E, Pronounced vacuolization of the constituent tumor cells is featured in this field (hematoxylin-eosin, original magnification ×600). F, Palpebral carcinoma in situ adjacent to the invasive mass displays focal vacuolization (arrowheads) (hematoxylin-eosin, original magnification ×200).
vision due to a mucinous discharge. Magnetic resonance imaging was undertaken to check for extension of the lesion, which disclosed diffuse thickening of the left upper eyelid back to, and possibly including, the superior rectus muscle and lacrimal gland. The patient subsequently underwent surgery to remove a 2.5-cm lesion from the tarsus of the left upper eyelid (Figure 1B). Frozen sections stained with oil red O were obtained during surgery because the histopathologic features suggested a possible sebaceous carcinoma. The findings were negative.

Histopathologically, the tumor cells grew in cords, ribbons, and lobules with scattered foci of central necrosis (comedonecrosis pattern imitative of sebaceous carcinoma) (Figure 1C and D). The tumor cells were eosinophilic without overt keratinization and exhibited cytoplasmic hydropic and vacuolar changes (Figure 1E). A carcinoma in situ component was detected at the edges of the invasive portion and displayed identical rarefied cells (Figure 1F). Staining results with periodic acid–Schiff stain for glycogen and Alcian blue and mucicarmine stains for intracytoplasmic mucin (Figure 2A) were negative. Cytokeratin 7 and epithelial membrane antigen immunostaining was positive (Figure 2B and E); adipophilin for lipid and androgen receptor were negative (Figure 2C and D), except for small adipophilin-positive granules in regions of necrosis (Figure 2C, inset). Ki-67 for premiotic cells revealed nuclear staining in about 25% of cells (Figure 2F). Polymerase chain reaction tissue analysis for human papillomavirus (HPV) types disclosed positivity for HPV 16 (Roche Cobas 4800 high-risk HPV test). A diagnosis of poorly differentiated squamous cell carcinoma with clear-cell features was made. The patient had negative findings on sentinel lymph node biopsy and received adjuvant radiotherapy as a precaution. She has been tumor free for 10 months.

Discussion | Clear-cell squamous carcinoma, which usually occurs in the epidermis but may occasionally be seen in mucous membranes, is less prone to metastasis than sebaceous carcinoma but has received virtually no attention in ophthalmology. The cause of the clear-cell change is unknown but not due to glycogen. The intermediate-weight cytokeratin 7–positive staining of the vacuolated cells is consistent with a conjunctival squamous cell origin, which in the current case proved

Figure 2. Mucicarmine and Immunohistochemical Staining Results

A, The mucicarmine stain fails to demonstrate positive magenta staining of either the necrotic cell clusters or surrounding viable cells (mucicarmine stain, original magnification ×100). B, Epithelial membrane antigen positivity is demonstrated in the cell membranes of the infiltrating tumor cells. The surrounding lymphocytic host response is nonstaining (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×400). C, Androgen receptor nuclear negativity characterizes the entire tumor (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×400). Inset, Androgen receptor nuclear positivity is seen in a small lobule of a meibomian sebaceous gland (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×400). D, Adipophilin positivity (arrowheads) for lipid identification was identified only rarely in tumor zones adjacent to necrosis (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×400). E, Cytokeratin 7 (intermediate weight) is strongly and uniformly present in the tumor cells (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×400). Inset, Same observation around a necrotic focus (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×150). F, Ki-67 nuclear positivity for detecting premiotic DNA synthesis was observed in around 25% of the tumor cells (immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, original magnification ×200).
to be associated with HPV 16. Higher-weight cytokeratins are encountered in the epidermis as opposed to mucous membranes.2,3 The 2 major differential diagnoses were sebaceous and mucoepidermoid carcinomas.4 Sebaceous carcinoma was excluded by oil red O cytoplasmic negativity and immunohistochemical stains that demonstrated negativity for both adipophilin (except for faint focal positivity in necrotic zones) and androgen receptors.5,6 Sebaceous carcinomas are 100% positive for androgen receptors.7 Mucoepidermoid carcinoma was excluded by negative Alcian blue and mucicarmine stains.8 Cutaneous squamous cell carcinomas of epidermal origin are 100% androgen receptor negative, but conjunctival dysplasias may rarely be focally positive.9 Immunohistochemistry can therefore be helpful in distinguishing clear-cell squamous carcinoma from sebaceous cell carcinoma. Our findings should also help to resolve the controversy over whether sebaceous carcinoma can arise primarily in the conjunctival epithelium. Previous reports of this entity may in fact have been examples of clear-cell squamous carcinomas in situ. Accurate early diagnosis separating intraepithelial clear-cell squamous and sebaceous carcinomas should lead to improved clinical management of these disparate conditions.

Ali Rashid, MBChB
Frederick A. Jakobiec, MD, DSc
John T. Mandeville, MD

Author Affiliations: David G. Cogan Laboratory of Ophthalmic Pathology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston (Rashid, Jakobiec); Eye Health Services, Quincy, Massachusetts (Mandeville).

Corresponding Author: Frederick A. Jakobiec, MD, DSc, David G. Cogan Laboratory of Ophthalmic Pathology, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114 (fred.jakobiec@meei.harvard.edu).

Published Online: May 22, 2014. doi:10.1001/jamaophthalmol.2014.971.

Author Contributions: Dr Jakobiec had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Jakobiec, Mandeville.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Rashid, Jakobiec.

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: All authors.

Study supervision: Jakobiec.

Conflict of Interest Disclosures: None reported.


Effect of Topical Rebamipide on Human Conjunctival Goblet Cells

The conjunctival epithelium contains mucin-secreting goblet cells, which are essential for maintenance of a healthy ocular surface.1 It has been demonstrated that topical administration of rebamipide, an antiulcer agent, increases the mucin level of the tear film and improves the ocular surface in dry eye syndrome.2 Indeed, rebamipide increased the number of goblet cells in rabbit and murine conjunctivas in vivo.3,4 Rios et al demonstrated that rebamipide led to proliferation of cultured rat conjunctival goblet cells,5 subsequently stimulating secretion from the cells.6 However, there has been no evidence that rebamipide exerts a strong action on human goblet cell behavior. This is the first report, to our knowledge, showing markedly increased goblet cells after administration of topical rebamipide in a patient with conjunctival dysplasia.

Report of a Case | A man in his late 70s had conjunctival hyperemia in the left eye. He was referred to our hospital because a conjunctival tumor was initially observed at a clinic. His visual acuity was 20/25 OS and his intraocular pressure was normal. Slitlamp examination revealed a pinkish tumor located in the nasal bulbar conjunctiva (Figure 1A). Indocyanine green angiography of the anterior segment demonstrated a markedly stained lesion corresponding to the tumor (Figure 1B). Dilated vessels associated with the tumor extended to the cornea (Figure 1B). The right eye was healthy. Because carcinoma in situ was initially suspected, the conjunctival tumor and the