
Neoplasms showing apocrine differentiation arise rarely in the ocular region, usually deriving from Moll glands of the eyelid. When they occur, they frequently cause clinical and pathological diagnostic problems, including the histopathological distinction between benignity and malignancy. We describe the clinical and pathological features of 5 cases, all in men, emphasizing their possible confusion with common eyelid lesions and illustrating a spectrum from benign to malignant pathological findings.

Report of Cases. Case 1. A 40-year-old man had an enlarging 2- to 3-mm nodular mass of the left lower eyelid at the lateral canthus (Figure 1A). Following wedge resection, pathological examination revealed a discrete, incompletely excised, dermal tumor (Figure 1B). Collections of acinar and tubular structures were lined by 2 layers of uniform cuboidal cells, showing apical snouts of decapitation secretion (Figure 1C and D). There were no mitotic figures or atypia. The diagnosis was Moll gland adenoma.

Case 2. A 40-year-old man had a nodular flesh-colored mass on the left lower eyelid and extending to the gray line. Histopathological examination showed a well-circumscribed intradermal nodule with ductal connections to the base of the hair follicles. Dense collections of acinar and tubular structures contained areas of myxoid change. Lumina were lined by 1 to 2 layers of uniform cuboidal-to-columnar cells with apical snouts. There were no mitotic figures or atypia. Periodic acid–Schiff stain delineated the periglandular basement membrane (Figure 2A). Colloidal iron and Alcian blue stains for glycosaminoglycans showed widespread stromal positivity. The immunostain gross cystic disease fluid protein 15 (GCDFP-15) was positive on the inner epithelial layers (Figure 2B) whereas the apocrine-specific immunostain B72.3 was negative. Immunostaining for smooth muscle actin was positive in the outer myoepithelial layers. The diagnosis was tubular apocrine adenoma.

Figure 1. Case 1 shows an adenoma of glands of Moll. A, Left lateral eyelid margin lesion at the lateral canthus. B, Cystic and tubular structures within a large tumor nodule in the middle compartment of the eyelid (hematoxylin-eosin, original magnification ×6.6). C, Snouts of decapitation secretion (arrow) (hematoxylin-eosin, original magnification ×132). D, Many of the cystic structures have intraluminal secretion (arrow) (hematoxylin-eosin, original magnification ×66).
Case 3. A 66-year-old man underwent incision of a presumed chalazion of the left lower eyelid. Thirteen years later, he reported 3 years of swelling, bleeding, and ulceration in the same area. A 5 × 6-mm bluish area of infraciliary thickening extended onto the eyelid margin with madarosis (Figure 3A). Lymphadenopathy was absent.

A biopsy showed tumor nodules, in dense collagenous stroma, containing irregular tubular proliferations of bland apocrine cells with apical snouts (Figure 3B). The tumor was continuous with the surface epithelium. The subsequently resected eyelid margin contained a nodular tumor in the tarsal region. There was focal transformation of the apocrine duct–like epithelium to larger, paler tumor cells with pleomorphic nuclei, prominent nucleoli, and 0 to 3 mitotic figures per high-

Figure 2. Case 2 shows a tubular apocrine adenoma. A, Acinar tubular structures show lumina lined by eosinophilic columnar cells with snouts (periodic acid–Schiff, original magnification ×132). B, Luminal cells and snouts stain positive for apocrine marker (gross cystic disease fluid protein 15, original magnification ×66).

Figure 3. Case 3 shows a papillary apocrine hidradenoma that transformed to apocrine adenocarcinoma. A, A bluish mass on the left lateral lower eyelid margin with recent bleeding (arrow). B, The tumor from the first biopsy shows mainly bland nuclei (hematoxylin-eosin, original magnification ×132). C, Transformation of the apocrine epithelium to larger tumor cells with nucleoli and mitotic figures (arrow) (hematoxylin-eosin, original magnification ×132). D, Tumor cells stain positive for apocrine marker (gross cystic disease fluid protein 15 [red chromogen], original magnification ×66).
power field (Figure 3C). A few double-layered ducts near the tumor showed focal papillary proliferation with atypia. The tumor cells were strongly positive for GCDFP-15 (Figure 3D) and high-molecular-weight cytokeratin. They were negative for S100 protein and carcinoembryonic antigen. Eccrine cells in the section were negative for GCDFP-15 and positive for S100 protein. The biopsy diagnosis was hidradenoma papilliferum but was amended to apocrine adenocarcinoma on the subsequent resection.

Case 4. A 53-year-old man noted recent enlargement of a 5-year-old right lower eyelid nodule. A firm, dome-shaped, infraciliary mass exhibited prominent telangiectatic vessels (Figure 4A). The clinical diagnosis was basal cell carcinoma.

Biopsy showed a multinodular intradermal tumor with adjacent hair follicles and Moll gland duct. The larger nodules were cystic, were lined with a papillary apocrine-type epithelium surrounding fibrovascular cores (Figure 4B), and contained 3 mitotic figures per high-power field. The solid areas showed an adenoid pattern with round-to-oval, slightly irregular, vesicular nuclei and small nucleoli. The fibrous stroma contained granulomatous inflammation, hemosiderin, and cholesterol. Mucin was prominent in the abnormal duct-like walls (Figure 4C). Staining for GCDFP-15 was positive within the tumor cells (Figure 4D) and alveolar-like spaces, but staining for S100 protein was negative. The diagnosis was apocrine papillary cystadenoma with atypia (low-grade apocrine adenocarcinoma).

Case 5. A 71-year-old man noted recurrence of a left lower eyelid cutaneous neoplasm excised 6 months previously without histopathological examination. The nontender, polycystic, 2 × 2-mm, grayish tumor at the midportion of the eyelash line showed telangiectatic vessels (Figure 5A). Lymphadenopathy was absent. The clinical diagnosis was basal cell carcinoma.

Following wedge resection of the eyelid margin, histopathological examination showed a well-circumscribed intradermal tumor (Figure 5B) comprising papillary islets of moderately pleomorphic epithelial cells (Figure 5C). Adjacent dilated double-layered apocrine ducts showed a pleomorphic papillary tumor arising from their walls (Figure 5C, inset). Microcysts stained positively for mucin. Staining for GCDFP-15 was positive within the cysts and tumor cell cytoplasm whereas staining for S100 protein was negative. There was patchy iron posi-
tivity of the tumor cells. The mitotic rate was low. The diagnosis was apocrine adenocarcinoma, which was completely excised.

Two of these 5 male patients had incomplete excisions. None have had metastases in the past 9 to 15 years (Table).

Comment. Unlike the common apocrine hidrocystomas among the cilia, Moll gland adenomas and adenocarcinomas are rare.\(^1\) Classification of sweat gland neoplasms traditionally separated them into eccrine or apocrine origin and derivation from ductal or secretory portions of the glands. An alternate classification of apocrine neoplasms based on their common embryological origin from the folliculo-sebaceous-apocrine germ\(^2,3\) has resulted in a controversial re-interpretation of some eccrine tumors as apocrine.\(^1,2\) Nomenclature of benign and malignant apocrine tumors, while elaborate and colorful, has been unsystematic and confusing. Clinically, apocrine and eccrine eyelid tumors are indistinguishable, as both may exhibit a bluish hue,\(^1\) a 5- to 10-mm diameter, bleeding, ulceration, or serosanguineous exudation.\(^1,2\) Eyelid marginal location is

Figure 5. Case 5 shows an apocrine adenocarcinoma. A, Recurrent small gray nodule just below the central left lower eyelash line. B, Papillary dermal tumor with adjacent apocrine gland above (arrow) (hematoxylin-eosin, original magnification $\times4.29$). C, Adenocarcinoma has pleomorphic epithelial cells (hematoxylin-eosin, original magnification $\times132$). Inset, A pleomorphic papillary tumor arises from the double-layered apocrine duct wall (hematoxylin-eosin, original magnification $\times33$).
characteristic of apocrine origin because Moll gland ducts empty into the cilial follicular infundibulum. Unless there is a blue color or serous discharge, however, most of these features suggest—and are misdiagnosed as—the common chalazion or basal cell carcinoma.

The principal diagnostic histopathological feature of apocrine glandular differentiation is decapitation secretion from cuboidal cells having eosinophilic cytoplasm, often with intracellular periodic acid–Schiff–positive and diastase-resistant granules containing iron. Tumors of eccrine glandular differentiation show pale cells without decapitation secretion, forming simple tubules. Tumors of either differentiation contain double layers of inner cuticular and outer flat epithelial cells and cannot be distinguished from one another by simple light microscopy, prompting assistance from immunohistochemistry.

Although antibodies for the apocrine epithelium derived from cystic breast disease fluid (GCDFP-15) are helpful, they may also stain some eccrine-derived tumors. The apocrine-specific marker B72.3 is problematic, as not all apocrine cells express this antigen. The murine antimelanocyte antibody IKH-4, staining eccrine but not apocrine secretory coils, is not readily available. Similarly, S100 protein usually stains eccrine but not apocrine tumors. Complicating the situation, immunohistochemistry and electron microscopy have demonstrated eccrine, apocrine, and sebaceous cells within a single tumor, suggesting pluripotentiality of the adnexal glandular epithelium. Human “apocrine glands” actually derive at puberty from eccrine precursors in the axilla, scalp, and pubic areas. Despite the murky distinctions between eccrine and apocrine neoplasms, some investigators continue to use the traditional classification.2

The potential for malignant transformation in Moll tumors is uncertain owing to few reports of apocrine carcinomas and scant diagnostic criteria. Since the case reported by Stout and Cooley7 in 1951, only 9 cases of Moll gland adenocarcinoma have been published. Such tumors in our cases 3, 4, and 5 were slow growing and difficult to categorize but were deemed malignant because of the principal histological features of a peripheral infiltrative pattern and nuclear atypia. Indolent tumors may recur and metastasize to local nodes. Only 1 case has shown highly aggressive behavior with metastasis to cervical nodes and bones.9

Prognosis of these rare tumors is indeterminate, although most patients appear to survive following surgical extirpation. Our 3 patients with adenocarcinoma had well-differentiated tumors, and all of them are alive and well from 9 to 15 years following the last surgery.

Apocrine glandular function is unknown, but research suggests that protein-bound hexanoic acids are released by cutaneous diphtheroids, producing mammalian pheromones.10 These compounds are much lower in concentration in the eyelids than in the axilla, but they may contribute to one's “odor signature.” Perhaps an atavistic phenomenon, these cells produce pheromones that are, at least in many animals, signatures of family identification.

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Table. Summary of Cases

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y</th>
<th>Location of Lesion</th>
<th>Duration</th>
<th>Diagnosis</th>
<th>Malignant</th>
<th>GCDFP-15 Staining</th>
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<tr>
<td>1/M40</td>
<td>Left lateral canthus</td>
<td>Several months</td>
<td>Adenoma of glands of Moll</td>
<td>No</td>
<td>Test not performed</td>
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<tr>
<td>2/M40</td>
<td>Left lower lid</td>
<td>1 y</td>
<td>Tubular apocrine adenoma</td>
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<td>+</td>
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<tr>
<td>3/M66</td>
<td>Left lower lid</td>
<td>10 y, Additional 4 mo</td>
<td>Papillary apocrine hidradenoma</td>
<td>No</td>
<td>+</td>
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<tr>
<td>4/MS3</td>
<td>Right lower lid</td>
<td>5 y</td>
<td>Apocrine adenocarcinoma</td>
<td>Yes</td>
<td>+</td>
</tr>
<tr>
<td>5/M71</td>
<td>Left lower lid</td>
<td>6 mo</td>
<td>Apocrine adenocarcinoma</td>
<td>Yes</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: GCDFP-15, gross cystic disease fluid protein 15; +, positive.