

Case Report

Tubular apocrine adenoma of the eyelid – A case report and literature review



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Abstract

Tubular apocrine adenoma is a rare benign adnexal neoplasm most commonly identified in the scalp, composed of a dermal proliferation of apocrine tubules in a background of hyalinized stroma. Tubular apocrine adenoma can be a component of various sweat gland tumors and can also morphologically overlap with other sweat gland neoplasms. Isolated tubular apocrine adenoma arising in the glands of Moll is exceedingly rare, with only 4 previously reported cases. We present a 63-year-old male with tubular apocrine adenoma of the left upper eyelid, which recurred following initial incomplete excision. Although the lesion showed focal morphologic similarity to the apocrine variant of pleomorphic adenoma (chondroid syringoma), the diagnosis of tubular apocrine adenoma was supported by fluorescence in situ hybridization studies, which demonstrated absence of *PLAG1* and *HMG2* gene rearrangements seen in pleomorphic adenoma. This case illustrates the clinical, microscopic and immunohistochemical features of tubular apocrine adenoma. The recent advances in our understanding of the molecular genetics of tubular apocrine adenoma and related tumors, and how these advances shape the evolving classification of sweat gland tumors are reviewed.

Keywords: Eyelid, Tubular apocrine adenoma, Chondroid syringoma, Pleomorphic adenoma, *PLAG1*, *HMG2*

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Introduction

Tubular apocrine adenoma is a rare benign adnexal neoplasm of apocrine derivation, which has been typically described in the scalp. This tumor is characterized histopathologically by a circumscribed intradermal proliferation of tubules lined by an apocrine epithelial bilayer in a background of hyalinized stroma.^{1,2} Tubular apocrine adenoma can be a component of other apocrine gland tumors, including syringocystadenoma papilliferum and apocrine cystadenoma. The term “tubulopapillary cystic adenoma with

apocrine differentiation” has been coined by Ansai and colleagues to describe the morphologic spectrum of these hybrid lesions.³ Isolated tubular apocrine adenoma is exceedingly rare in the eyelid with only 4 previously reported cases.^{1–4} Herein, we describe a patient with tubular apocrine adenoma arising in the gland of Moll and discuss the clinical, microscopic, immunohistochemical, and molecular genetic features of this neoplasm. The Institution Ethics Review Committee approval was waived for this retrospective case report study. This research was conducted in conformity with the Helsinki Declaration and HIPPA regulations.

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Fig. 1. Tubular apocrine adenoma, clinical features. A well-circumscribed, skin-colored, non-ulcerated, dermal-based nodule at the left upper eyelid margin adjacent to the lacrimal punctum, associated with focal madarosis and telangiectasia.

Case report

A healthy 63-year-old-white male was referred for evaluation of a left upper eyelid lesion, which recurred following

excision 3 years previously. Pathologic diagnosis of "cauterized seborrheic keratosis" was rendered at the time of initial surgery. Examination of recurrent lesion demonstrated an $8 \times 7 \times 3$ mm well-circumscribed, skin-colored, non-ulcerated, dermal-based nodule at the left upper eyelid margin adjacent to the lacrimal punctum, associated with focal madarosis and telangiectasia (Fig. 1). The remainder of the eye examination was unremarkable. The lesion was excised via full-thickness wedge resection of the eyelid with frozen section control of margins followed by cryotherapy to the surgical margins and reconstruction.

Histopathologic evaluation demonstrated a circumscribed proliferation of variably sized ductules lined by an apocrine-type bilayer with decapitation secretion and luminal eosinophilic-to-amphophilic secretory material in a background of hyalinized stroma. Scattered foci of stromal spindle cell proliferation associated with myxoid matrix, suggestive of myoepithelial differentiation, and rare foci of squamous metaplasia were also identified. Prior surgical site changes were present in the adjacent stroma. There was no evidence of appreciable nuclear atypia or mitotic activity. No necrosis or perineural invasion were identified (Fig. 2).

A panel of immunohistochemical stains showed that the luminal cells in the ductules immunoreacted strongly and diffusely with BRST-2 and mammaglobin and focally with androgen receptor antibodies, compatible with apocrine differentiation. The outer layer of the ductules expressed S-

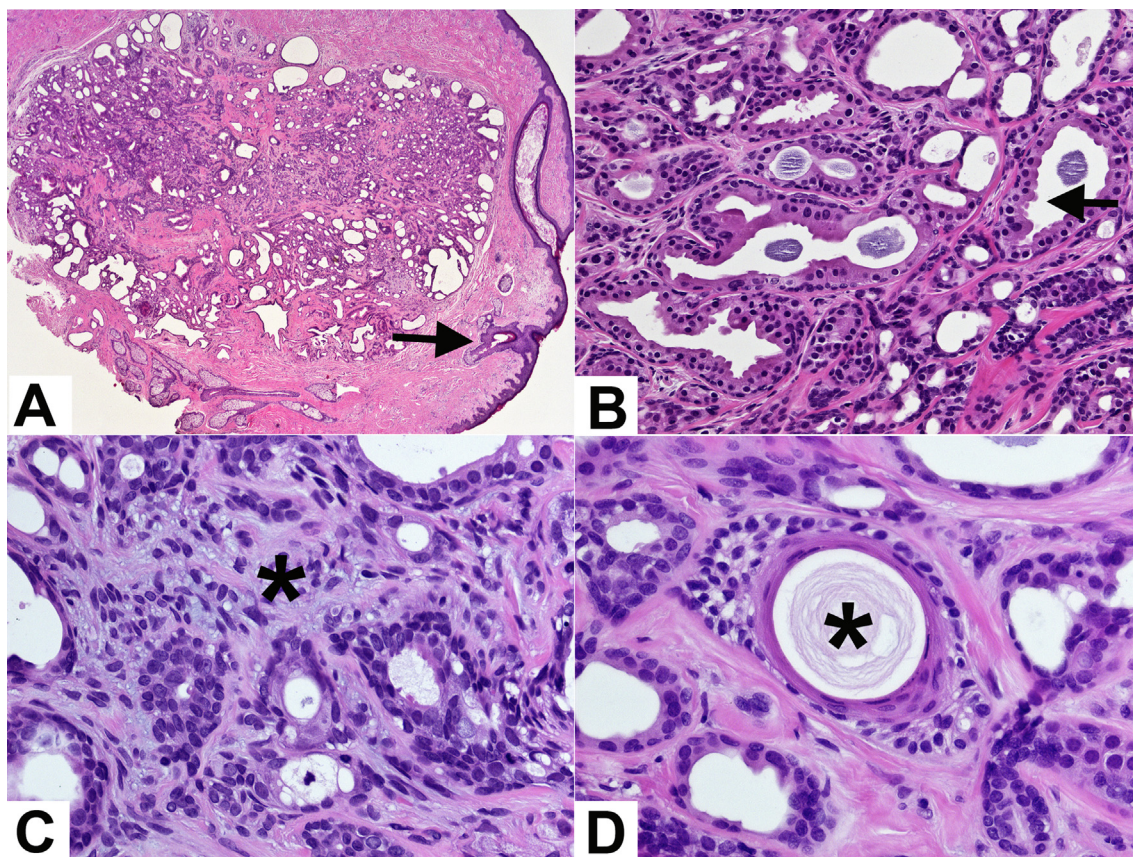


Fig. 2. Tubular apocrine adenoma, histopathologic features. (A) A circumscribed dermal-based proliferation of variably sized tubules adjacent to the cilia (arrow). (B) The lesion is composed predominantly of irregular ductules lined by an apocrine-type bilayer with apocrine decapitation secretion (arrow) and luminal eosinophilic-to-amphophilic secretory material in a background of hyalinized stroma. (C) A focus of spindle cell proliferation in a myxoid background (asterisk) is present in the stroma. (D) Focal squamous metaplasia with luminal keratin (asterisk) is identified. [Stain, hematoxylin-eosin; original magnification $\times 5$ (A), $\times 50$ (B) $\times 100$ (C, D).]

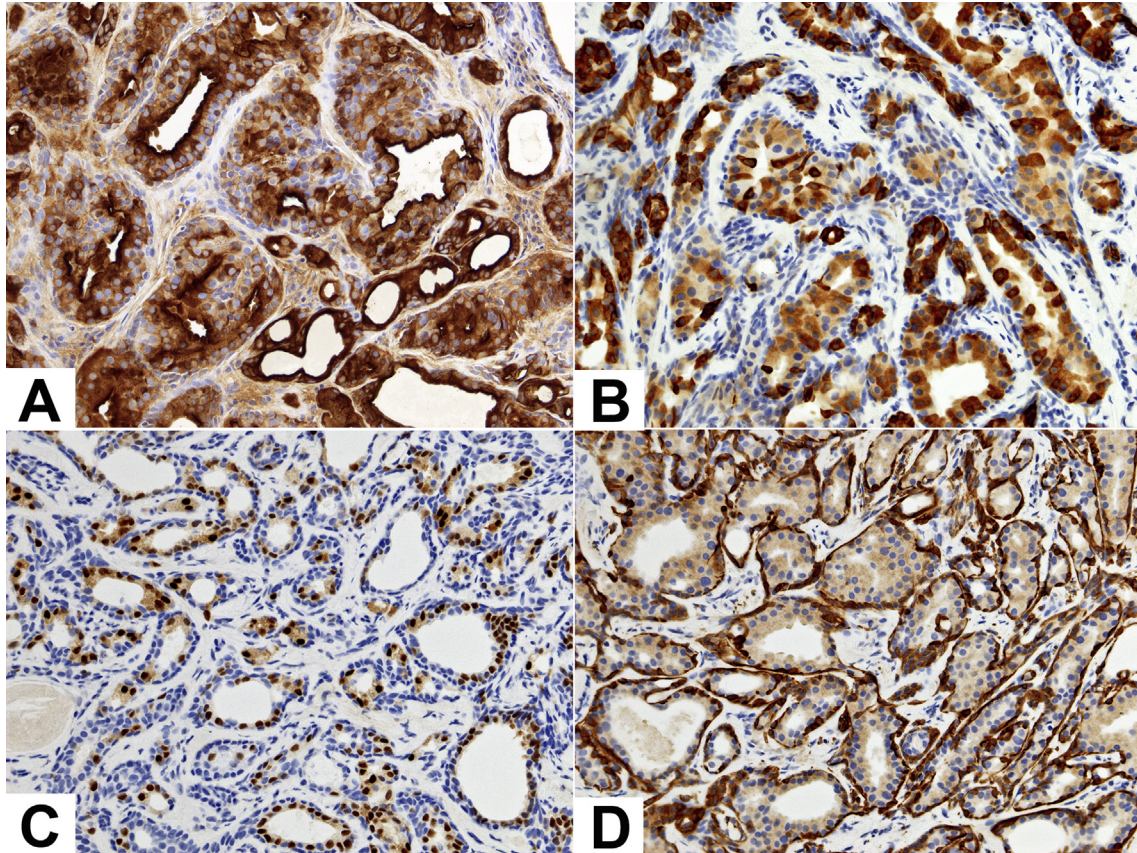


Fig. 3. Tubular apocrine adenoma, immunohistochemical features. (A) The luminal layer of the apocrine bilayer expresses cytoplasmic BRST-2, (B) cytoplasmic mammaglobin and (C) nuclear androgen receptors. (D) Calponin highlights the outer myoepithelial layer in the ductules and is negative in the adjacent stroma. [Stains, BRST-2 (A), mammaglobin (B), androgen receptors (C), calponin (D); all images, original magnification $\times 50$].

100 and calponin, compatible with myoepithelial differentiation. Focal expression of S-100, but not calponin was also present in the spindle cell stromal component of the lesion (Fig. 3). Fluorescence in situ hybridization studies for *PLAG1* and *HMGA2* gene rearrangements, performed to more definitively distinguish between the apocrine variant of pleomorphic adenoma and apocrine tubular adenoma, were both negative, supporting the diagnosis of apocrine tubular adenoma.

Discussion

Isolated eyelid tubular apocrine adenoma is an extremely rare benign apocrine neoplasm, with only 4 cases reported in the literature.^{1–4} The 3 lesions with documented clinical history all presented with features of a well-circumscribed nodule involving the lower (2/3) or upper (1/3) eyelid in 2 females and 1 male at a mean age of 47 years (range 38–63).^{1,2,4} Recurrence was noted in one of 3 lesions.¹ Our male patient similarly presented with a well-circumscribed nodule in the upper eyelid, which recurred following incomplete excision.

While rare in its isolated, pure form, tubular apocrine adenoma can morphologically overlap with papillary eccrine adenoma, manifesting as a spectrum lesion. Unlike tubular apocrine adenoma, which preferentially involves the skin of the head and neck region, papillary eccrine adenoma is most commonly seen in the extremities and, as the name implies, is a neoplasm with eccrine differentiation that lacks apocrine decapitation secretion and features intraluminal papillary or micropapillary growth.⁵ However, hybrid tumors with mor-

phologic features of both tubular apocrine adenoma and papillary eccrine adenoma have been recognized.⁶ Recent molecular genetic studies have demonstrated *BRAF*^{V600E} mutations in 60% of tubular apocrine adenomas and in 78% of papillary eccrine adenomas, providing further evidence for a genetic link between these neoplasms.⁵ In recognition of the morphologic continuum between these two lesions, the term “tubular papillary adenoma” has been coined and incorporated into the World Health Organization classification of skin tumors.⁷

In addition to its morphologic overlap with papillary eccrine adenoma, tubular apocrine adenoma can be a component of other apocrine tumors, including syringocystadenoma papilliferum (characterized by papillary projections of apocrine epithelium, surrounded by an intense plasma cell stromal infiltrate) and apocrine cystadenoma (featuring a cystic structure lined by apocrine epithelium with papillary luminal projections).^{3,8} This observation has led Ansai and colleagues to suggest that the unifying term, “tubulopapillary cystic adenoma with apocrine differentiation”, should be used to describe the morphologic spectrum of these lesions.³ This conclusion is supported by the recent molecular genetic studies demonstrating *HRAS*, *KRAS*, and *BRAF*^{V600E} mutations in syringocystadenoma papilliferum, confirming the genetic link between this neoplasm and tubular apocrine adenoma, papillary eccrine adenoma, and tubular papillary adenoma.^{9,10}

The lesion in our patient demonstrated focal spindle cell stromal proliferation in a myxoid background and squamous

metaplasia reminiscent of apocrine variant of pleomorphic adenoma (chondroid syringoma), a rare adnexal neoplasm, which can arise in apocrine sweat glands. Similar to its salivary and lacrimal gland counterpart, the chondroid syringoma is characterized by proliferation of sweat gland ductules suspended in a myxoid, chondroid, adipocytic, or fibrous stroma,¹¹ which harbors *PLAG1* rearrangements in 37–72% of cases.¹² The apocrine variant of chondroid syringoma features glandular epithelial component with apocrine differentiation. The distinction between chondroid syringoma and tubular apocrine adenoma is important due to prognostic implications. Both tubular apocrine adenoma and chondroid syringoma can recur following incomplete excision. However, while malignant transformation has been documented in chondroid syringoma, malignant behavior has not been reported in isolated tubular apocrine adenoma.¹³ It must be noted that while the presence *PLAG1* and *HMGA2* rearrangements confirms the diagnosis of pleomorphic adenoma, the absence of these rearrangements does not unequivocally exclude pleomorphic adenoma. The diagnosis of tubular apocrine adenoma in our patient was rendered predominantly based on morphology and was further supported by the fluorescence in situ hybridization study results.

This case illustrates the clinical features, biologic behavior, and histopathologic findings of tubular apocrine adenoma arising in the glands of Moll and highlights the frequent morphologic overlap between various sweat gland tumors. The unraveling genetic landscape of sweat gland neoplasms influences the continually evolving classification of these lesions and, in some cases, can be diagnostically useful.

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Conflict of interest

The authors declared that there is no conflict of interest.

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