

Apocrine Hidrocystoma with  
Proliferative Features: Apocrine  
CystadenomaJonathan L Yao<sup>1\*</sup> and Robert G Phelps<sup>2</sup><sup>1</sup>Dermatopathology, GPA-Aurora Diagnostics, USA<sup>2</sup>Department of Dermatopathology, Mount Sinai Medical Center, New York, USA

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## Abstract

We present seventeen cases of apocrine hidrocystoma, ten of which had pseudopapillary and solid areas of proliferation. The lesional cells were examined for the extent and intensity of immunohistochemical staining for neuroendocrine and endocrine markers. Of the ten hidrocystomas with adenomatous features, eight cases (80%) displayed immunoreactivity to Estrogen (ER) and Progesterone Receptors (PR). None of the cases showed staining for chromogranin. Conversely, none of the cases of classic apocrine hidrocystoma (0 of 7) exhibited staining for ER, PR, or chromogranin. Furthermore, all cases of hidrocystomas with and without proliferative features, behaved in a benign fashion without any recurrence. In conclusion, hidrocystomas with proliferative features are benign lesions, and we have shown this variant of apocrine hidrocystoma to have a novel staining pattern with ER and PR which has not previously been described. In addition, we offer further support based on the histological features and this unique staining pattern to the hypothesis that apocrine hidrocystomas, in particularly the proliferative variant, may be within the sequence of adenoma to carcinoma for Endocrine Mucin-Producing Sweat Gland Carcinoma (EMPSGC).

## Introduction

Hidrocystomas are benign lesions, commonly occurring in the peri-orbital region, with a female predilection. Occurrences at other facial regions such as the cheek, chin and lips, and non-facial locations have also been reported [1,2,3]. Hidrocystomas clinically present as small, 1-6 mm, cystic dome-shaped lesions, with a slight blue-brown pigmentation [1]. These lesions are often multilocular. These lesions consist of dilated cysts in the dermis and are at times adjacent to eccrine glands and apocrine glands. The cyst lining is composed of double-layered cuboidal to columnar cells. The myoepithelial layer may be difficult to discern on Hematoxylin and Eosin (H&E) stained slides. Papillary outgrowth and adenomatous hyperplasia are not usually present. Proliferative features, however, have been described in these lesions [2]. Some authors have used the term "cystadenoma" to describe hidrocystomas with adenomatous hyperplastic features within the cystic spaces [2,3]. A review of the literature has revealed that these lesions have a benign course despite focal cellular atypia and pleomorphism. In addition, neuroendocrine, ER and PR immunohistochemical profiling have not been previously evaluated in this lesion.

## Materials and Methods

We searched the archives within the Mount Sinai School of Medicine Dermatopathology department from 2007 to 2013. We found 248 cases of apocrine hidrocystoma and found 10 of which were apocrine cystadenoma. Clinical information included the patient's age, gender, and anatomic location of each lesion (Table 1). Hematoxylin and eosin-stained sections were available for all cases. We additionally chose seven classical apocrine hidrocystomas for comparison to the apocrine cystadenoma case. A total of seventeen cases (7 apocrine hidrocystoma and 10 apocrine cystadenoma cases) were then immunohistochemically profiled using ER, PR, chromogranin, and synaptophysin antibodies with the Vantana automated staining system. Each case was then reviewed by two dermatopathologists independently (JLY, RGP).

The histological features, including the presence of adenomatous hyperplasia (pseudopapillary, cribriform, solid, and hyperplastic growth) and the resulting immunohistochemical staining profile were then documented. Immunohistochemical profiles were graded as such: Grade 0 displayed 0% staining of the lesional epithelial cells; Grade 1 displayed 1-33% staining of the epithelial cells; Grade 2 showed 34-66% staining epithelial cells, and Grade 3 exhibited greater than 66% staining of the epithelial. Positive staining was considered valid when the cells in question had at least grade 1 (+1) staining of the appropriate region. In order for ER and PR stains to be considered valid, nuclear staining had to be present, while cytoplasmic staining was necessary for chromogranin and synaptophysin positivity.

**Table 1:** Pathologic and immunohistochemical features of classic apocrine hidrocystoma and those with proliferative features.

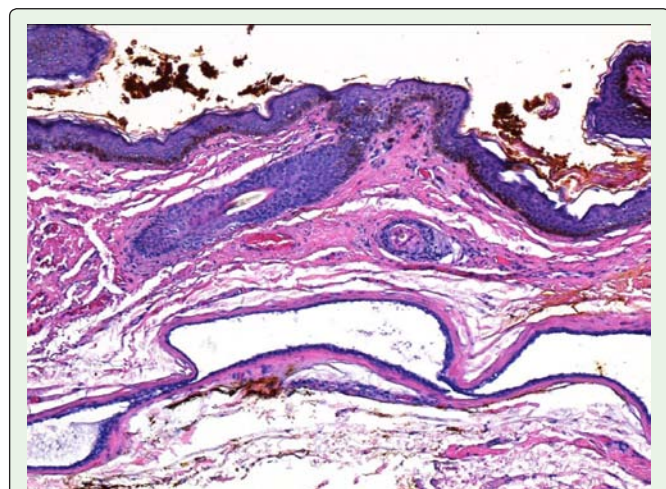
Case Number	Age	Gender	Location	Proliferative Features	ER	PR	Chromogranin	Synaptophysin
1	59	F	Eyelid	-	-	-	-	-
2	65	F	Eyelid	-	-	-	-	-
3	32	M	Canthus	-	-	-	-	-
4	55	F	Forehead	-	-	-	-	-
5	46	M	Forehead	-	-	-	-	-
6	52	F	Eyelid	-	-	-	-	-
7	51	F	Forehead	-	-	-	-	-
8	74	F	Scalp	+	3+	3+	-	-
9	67	F	Scalp	+	1+	1+	-	-
10	35	F	Lip	+	2+	2+	-	-
11	41	F	Scalp	+	-	-	-	-
12	58	M	Scalp	+	2+	2+	-	-
13	56	F	Forehead	+	1+	1+	-	-
14	55	F	Axilla	+	1+	1+	-	-
15	80	M	Eyelid	+	-	-	-	-
16	81	F	Eyelid	+	1+	1+	-	-
17	60	M	Eyelid	+	3+	3+	-	-

N/A: not applicable; ER, Estrogen Receptor; PR, Progesterone Receptor; -, no appreciable staining; 1+, 1-33% staining; 2+, 34-66% staining; 3+ > 67% staining.

**Results**

The immunohistological features of the seventeen cases are listed in Table 1. Seven cases fit the criteria for classic apocrine hidrocystoma. The lesions were cystic, uni- to multilocular and well circumscribed (Figure 1). Desmoplastic reactions and invasive foci were absent. The cyst walls were lined by single to double layer of cuboidal to low-columnar cells. The myoepithelial layer surrounding the luminal cells were noted at least focally in all lesions. Cytologic features included smooth nuclear outlines, low nuclear to cytoplasmic ratio, and lack of relative hyperchromasia. Mitotic figures and necrosis were inconspicuous.

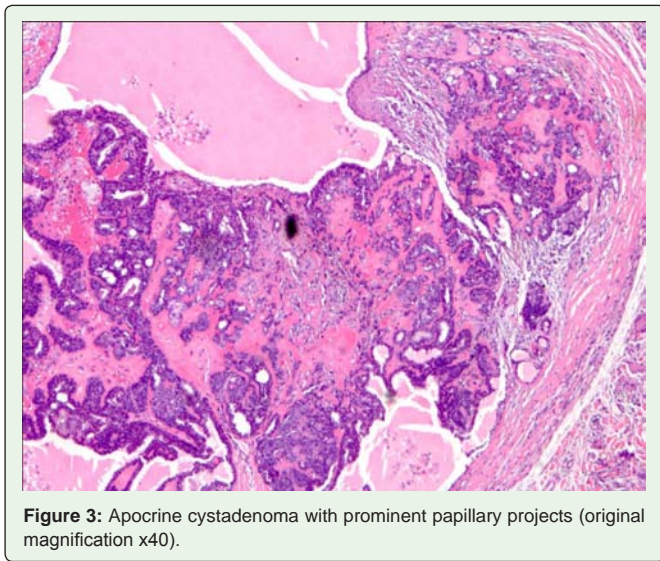
Ten of the seventeen lesions showed limited to diffuse adenomatous features. All were well circumscribed and no invasion was appreciated. The stroma showed delicate collagen fibers with no desmoplastic changes. All lesions showed cystic changes with foci of proliferative features that included pseudopapillary projections without fibrovascular cores, solid areas, and hyperplasia (luminal cells greater than four cells thick) (Figure 2 and 3). The proliferative glandular cells showed relative hyperchromasia and a mild increase in nuclear-to-cytoplasmic ratio greater than that of the non-proliferative regions. Nuclei were medium-sized and round-to-oval, with smooth nuclear membranes. Another lesion displayed a nodular



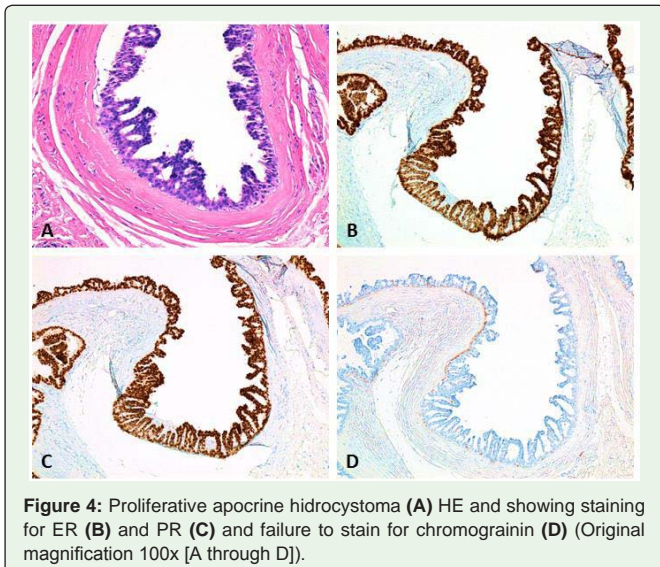
**Figure 1:** Classic apocrine cystadenoma with dilated cystic structured lined by one to two layers of benign appearing cuboidal cells.



**Figure 2:** Apocrine hidrocystoma with proliferative features. The cystic lining shows adenomatous hyperplasia with mild nuclear hyperchromasia (Original magnification x40 [A]).



**Figure 3:** Apocrine cystadenoma with prominent papillary projects (original magnification x40).



**Figure 4:** Proliferative apocrine hidrocystoma (A) HE and showing staining for ER (B) and PR (C) and failure to stain for chromograinin (D) (Original magnification 100x [A through D]).

growth pattern with aggregates of luminal cells greater than 50 cells, within the cyst. Yet another showed true papillae with fibrovascular core resembling that of hidrocystoma papillerferum. In addition, all ten of the hidrocystomas with adenomatous features showed foci of pseudopapillary structures. Within these proliferative regions, no mitoses, necrosis, or invasion was noted. The non-proliferative lining cells adjacent to the proliferations were distinct and had benign histology.

Immunohistochemical profiling was performed on all seventeen lesions. None of the purely cystic hidrocystoma lesions showed any staining for ER, PR, or neuroendocrine markers. Conversely, eight of the ten adenomatous cases (80%) showed staining for ER and PR in the hyperplastic regions. Two cases showed grade 3 staining pattern for the cells within the proliferative regions, positive in greater than 66% of these cells (case #8 and #17) (Figure 3). The cystic epithelium adjacent to the proliferation centers showed no staining for ER and PR. None of the seventeen cases had any positivity for neuroendocrine markers (Figure 3).

## Discussion

Clinically, apocrine hidrocystoma can appear flesh-colored or blue to dark blue mimicking pigmented basal cell carcinoma or melanoma [4]. Earlier nomenclature included terms like “black hidrocystoma” [5]. The bluish hue has been attributed to the Tyndall light affect and not to hemosiderin or melanin [6,7]. This lesion can also clinically resemble cyst, nevi, actinic keratosis and syringoma [5]. Apocrine hidrocystomas can present singularly or multiple [6,8]. These lesions commonly occur on the face; however, it can occur, though with less frequency, on sites bearing apocrine glands.

The term apocrine cystadenoma was first coined by Mehegran et al., and denotes papillomatous and adenomatous hyperplasia of the luminal cells in what would otherwise be considered an apocrine hidrocystoma. In a review of the literature, it is evident that many do not strictly adhere to the terminology. Apocrine hidrocystoma with adenomatous and papillomatous features presents clinically similar to that of its non-proliferative counterpart, and it is not possible to distinguish these two variants clinically. The proliferative variant also commonly occurs on facial skin but has been reported in the axilla, scalp, and groin regions as well [6,9]. Two reports documented that these lesions occurred adjacent to syringocystadenoma papilleferum and nevus sebaceous on the scalp [7]. None of our cases were associated with nevus sebaceous. Apocrine cystadenoma can also be seen in urogenital sites, where there are abundant apocrine glands. Two reports documented the lesion on the prepuce and four occurring on the penile shaft [10-12]. Hidrocystomas with proliferative features or apocrine cystadenomas are considered benign.

In one study of 21 apocrine lesions, hidrocystomas showed no nuclear atypia or appreciable mitotic activity. In the same study, the cystadenoma type with pseudopapillary growth displayed nuclear atypia in 4 of 12 cases (33.3%) and mitotic activity in 3 of 12 cases (25%) [2]. When looking at cystadenomas with true papillary growth, all 5 cases showed evidence of nuclear pleomorphism and hyperchromasia, and 4 of the 5 cases showed appreciable mitoses [2]. Despite concerning histological features of the proliferative cells, there have been no reports of metastasis or recurrence. Our 10 cases of hidrocystoma with proliferative features, all had a benign course with no recurrence, and all patients remained disease free of the lesion at 1 year follow up.

Histologically, apocrine hidrocystoma is distinguished from its non-proliferative counter by a papillomatous and or adenomatous growth pattern. The proliferative region may be diffuse or localized within the lesion [7]. In a study by Smith et al. 24 of the 50 apocrine cystadenomas showed true papillary structures with a central fibrovascular core [5]. PAS granules can sometimes be seen in the luminal cells [13]. Often, focal apocrine-type decapitation secretion can be seen. More often, however, due to the enlarging cyst, the luminal cells are compressed and apocrine secretion cannot be appreciated. These cystic lesions are lined by a myoepithelial cells highlighted by S100 and calponin. HMFG1 have been shown to stain proliferative luminal cells in a cystadenoma. The additional presence of luminal staining for CK7, K8, and K18 along with actin has been shown to be specific to apocrine cystadenoma [14]. However, no reports have documented ER and PR nuclear staining of apocrine hidrocystoma with proliferative features.

In the English literature thus far, we are the first to report ER/PR staining in apocrine hidrocystoma with proliferative features. ER and PR staining patterns are not found in normal apocrine glands. In 8 of the 10 of our cases with proliferative features, there is strong staining for both ER and PR equally. This staining is diffuse and strong to the adenomatous areas within the cystic lesion. The adjacent non hyperplastic bilayered cyst lining is negative for ER and PR. None of the 10 lesions showed any positivity for chromogranin (Figure 4).

It is of further interest that recently described entities Endocrine Mucin Producing Sweat Gland Carcinoma (EMPSGC) first describe by Fleider and later by Zembowicz, has shown histological, immunohistochemical, and clinical similarities to apocrine cystadenoma. Although the exact etiology of EMPSGC is not clearly defined, Zebowicz had suggested that apocrine hidrocystoma may be a precursor lesion [15]. No studies have yet examined his hypothesis. Clinically, both apocrine cystadenoma and EMPSGC occur commonly on facial skin. Both lesions histologically are represented by cuboidal cells with adenomatous growth pattern. In EMPSGC there is cytological atypia and infiltrative pattern that are not seen in apocrine cystadenoma. Our studies also examined these proliferative features with the same immunoprofile markers for EMPSGC. All published cases up to now of EMPSGC that were tested for the respected antibodies reported positivity for ER or PR (20/20) and at least one neuroendocrine marker: chromogranin (16/20); synaptophysin (17/18); and non-specific enolase (16/18) [15-20]. Our finding have shown that 80% of the cases of apocrine cystadenoma had focal to diffuse staining for ER and PR, however, none of the cells in either group exhibited positivity for neuroendocrine markers. The histological similarity between hidrocystoma with proliferative features and the new immunohistochemical finding shown in our study for ER and PR garner support for the possibility, as suggested by Zembowicz, that hidrocystomas may be part of the sequence of adenoma to carcinoma in EMPSGC. Furthermore, the gain of neuroendocrine immunohistochemical marker is an indication of carcinomatous transformation for apocrine cystadenoma.

In conclusion, we present 17 cases of hidrocystomas, 10 with proliferative features. None of the 10 proliferating hidrocystomas, or apocrine cystadenoma, recurred. The non-proliferative hidrocystomas fail to stain with ER, PR and chromograinin. Eight of the 10 proliferative hidrocystomas showed strong and diffuse staining for ER and PR in the adenomatous region. This finding has not been described previously and may offer support to Zembowicz's hypothesis that hidrocystomas are a precursor lesion to EMPSGC.

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