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Apocrine and eccrine hidrocystomas: a clinicopathological study

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Abstract

Introduction: Eccrine and apocrine hidrocystomas are uncommon, benign, cystic proliferations of the sweat glands usually located on the head and neck area.
Objectives: To describe the key clinical and histopathological characteristics of a large series of hidrocystomas in Greece to improve diagnostic accuracy, and to perform a historical review of the medical term *hidrocystoma*.
Methods: A case series of 22 hidrocystomas from 20 consecutive patients treated with surgery at University Hospital of Heraklion in Crete, Greece, from January 1, 1998 to January 1, 2020 was performed along with a comprehensive historical literature review of the term *hidrocystoma* and its corresponding term *hydatis* from ancient Greek literature to the present. Data were obtained from medical records. All patients had a histopathologically confirmed diagnosis of hidrocystoma. Formalin-fixed paraffin-embedded (FFPE) sections of 22 tumors of the 20 consecutive patients were retrieved from the pathology laboratory archive and stained for SMA, p63, and GCDFP-15 with immunochemistry and periodic acid–Schiff (PAS) histochemical stain.
Results: Overall, 22 hidrocystomas (11 apocrine and 11 eccrine hidrocystomas) surgically excised from 20 patients were included in this study. Of the 20 patients, 10 (50%) were male and 10 (50%) were female, with a mean age of 56 ± 15 years. Hidrocystomas commonly occurred on the eyelids (73%), inner canthus (9%), eyebrow (4.5%), neck (4.5%), nose (4.5%), and ear (4.5%). All apocrine hidrocystomas stained positive for SMA, GCDFP-15, CAM 5.2, PAS, and PAS-D. No recurrence was observed.
Conclusions: Here we have presented the clinicopathological characteristics of the largest case series of hidrocystomas in Europe and the Mediterranean region. Only apocrine hidrocystomas stained positive for SMA, GCDFP-15, CAM 5.2, PAS, and PAS-D.

Keywords: apocrine hidrocystomas, eccrine hidrocystomas, cystic proliferation, sweat glands, eyelid tumors

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Introduction

Hidrocystomas are rare, benign, watery cystic proliferations of the apocrine glands of the skin (1). Based on their histopathological findings, they are distinguished into apocrine and eccrine hidrocystomas (2). Apocrine hidrocystomas are cysts that are often multilocated with apocrine secretion (3, 4). Eccrine hidrocystomas are more likely to represent unilocular retention of sweat in a dilate duct or gland rather than a cystic neoplasm with no decapitation secretion (5). Hidrocystomas most commonly appear in adulthood as solitary, soft, dome-shaped, translucent papules or nodules. They are most often found on the eyelids, especially the inner canthus and occasionally elsewhere, such as the neck, trunk, penis, axillae, and anal region (6, 7). Surgical excision has been the treatment of choice for solitary lesions (8).

The literature on this topic is scant and is primarily composed of case reports. A few retrospective series have also been reported. In a bi-institutional study, Maeng et al. analyze 215 hidrocystomas in 107 patients, but they do not distinguish between apocrine and eccrine lesions due to inconsistent pathology reporting (9). Deprez and Uffer report 326 cases, but they also present apocrine and eccrine tumors as a whole. Moreover, their study is focused on eyelid tumors in general rather than hidrocystomas (10). Anzai et al. present a case report of an apocrine lesion along with a thorough literature review of apocrine hidrocystomas in Japanese studies between 1968 and 1998 (11).

To the best of our knowledge, there is no study on the clinicopathological features of hidrocystomas in Europe and the Mediterranean region. This study examines the clinical and histopathological characteristics of apocrine and eccrine hidrocystomas in a cohort of patients treated surgically in the Plastic Surgery Department at the University Hospital of Heraklion in Crete, Greece.

Patients and methods

Patients and procedures

A single-center retrospective longitudinal cohort study was conducted in the plastic surgery unit of the surgical oncology department at an academic tertiary hospital in Crete, Greece. Eligible were all patients with surgically excised and histologically confirmed hidrocystomas in a 22-year period, from January 1, 1998 to December 31, 2019. Clinical characteristics of patients were retrieved from patients' files. All paraffin-embedded tumors histologically diagnosed as apocrine or eccrine hidrocystomas were retrieved from our pathology department. In all cases, sections stained with hematoxylin and eosin were reviewed by the same dermatopathologist in our pathology department, and the original diagnosis was confirmed. Eccrine hidrocystoma was diagnosed in large uniloculated and dilated cysts devoid of papillary infoldings; the cyst wall was composed of either two layers of cuboidal cells typical of ductular epithelium, or one or two layers of flattened cells. Apocrine cystadenoma was diagnosed in uni- or multiloculated cysts with a wall composed of one or more layers

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of cuboidal to columnar cells, with at least focal decapitation secretion.

Immunohistochemistry

For immunohistochemistry (IHC) staining, 3-micron thick formalin-fixed paraffin-embedded (FFPE) tissue sections, placed on charged glass slides, were deparaffinized in xylene and rehydrated in a graded series of ethanols. Epitope retrieval was heat-induced in a steam pot in a solution buffered with EDTA at pH 8 for p63, with sodium citrate buffer at pH 6 for SMA for 15 minutes, and in a pepsin solution for 10 minutes at pH 2 for GCDFP. Endogenous peroxidase was blocked by applying UltraVision Hydrogen Peroxide Block (Thermo Fischer Scientific, Waltham, MA, USA), for 15 min. Nonspecific protein-binding sites were blocked with UltraVision Protein Block (Thermo Fischer Scientific) for 5 minutes. Sections were stained with mouse monoclonal antibody GCDFP-15, clone D6 (Biocare Medical, Pacheco, CA, USA, cat#CM113) at 1:100, with p63 mouse monoclonal antibody, clone DAK-P63 (DAKO, Santa Clara, CA, USA, cat# M7317) at 1:200, and with SMA mouse monoclonal antibody, clone 1A4 (Thermo Fischer Scientific, cat# MA1-06110), at 1:100 for 1 hour at room temperature (Table 1). Immunodetection was performed by means of the UltraVision Quanto Detection System HRP Polymer DAB (Thermo Fischer Scientific), according to the manufacturer's instructions. A solution of 3,3' diaminobenzidine Quanto Chromogen (Thermo Fischer Scientific) was used as a chromogen for PD-L1. Ultimately, the slides were rinsed with distilled water for 5 min and then counterstained with hematoxylin.

Sections of breast carcinoma were used as an external positive control for GCDFP-15 staining. Epidermis and blood vessel walls were the internal positive controls for p63 and SMA staining, respectively. Negative controls were used with all stainings.

Statistical analysis

Normal distribution was determined using histogram plots, box plots, and the Shapiro–Wilk test. Continuous data were normally distributed and are therefore presented in mean–standard deviation form. Categorical variables of both hidrocystoma types were compared with the two-tailed Fischer's exact test. Statistical significance was set at the 5% level. Descriptive statistics and data analyses were performed using SPSS 25 (IBM SPSS, Chicago, IL, USA).

Results

Our search yielded 22 hidrocystomas (11 apocrine and 11 eccrine hidrocystomas), surgically excised from 20 patients during the study period.

Of the 20 patients, 10 (50%) were male and 10 (50%) were female, with a mean age of 56 years (range 27–86, SD ± 15). Hidrocystomas commonly occurred on the eyelids (16/22, 73%), inner canthus (2/22, 9%), eyebrow (1/22, 4.5%), neck (1/22, 4.5%), nose (1/22, 4.5%), and ear (1/22, 4.5%). The mean size of all 22 hidrocystomas was 9.55 (SD ± 5.99) mm. Eccrine hidrocystomas and apocrine hidrocystomas had a mean size of 7.27 (SD ± 4.1) mm and 11.82 (SD ± 6.87) mm, respectively. The clinical characteristics of the 22 tumors are summarized in Tables 2 and 3. There was no association between type of hidrocystomas with sex ($p = 0.67$), age ($p = 0.67$), or location of lesions ($p = 0.35$).

The immunohistochemical characteristics of the 22 tumors are summarized in Figure 1 (tumors histologically diagnosed as apocrine hidrocystomas) and Figure 2 (eccrine hidrocystomas). Periodic acid–Schiff (PAS) staining was positive in all apocrine hidrocystoma cases. The secretory cells of all 11 apocrine hidrocystomas expressed GCDFP-15. The myoepithelial cells of apocrine hidrocystomas also expressed the p63 and SMA stains. Eccrine hidrocystomas stained negative for PAS, PAS-D, GCDFP-15, p63, and SMA.

None of our patients experienced a recurrence of the surgically excised hidrocystomas during the follow-up period, ranging from 12 to 24 months.

Discussion

Hidrocystomas are benign asymptomatic translucent to bluish dome-shaped small cystic proliferations of sweat glands common around the eyelids, usually solitary, sometimes multiple (1–4).

Hidrocystomas, as clinical entities, are obviously as old as mankind itself. In antiquity, the term *hydatis*, watery cyst, referred to any skin lesion with watery inflammation and encompassed all types of small cysts filled with water or sebum on the skin (12).

Table 1 | Antibodies and dilutions used in this study. Antigen retrieval was conducted by heating the sections in a steam pot in the indicated retrieval buffer for 15 min for p63 and SMA antibodies, and for 10 min for GCDFP-15. Tris-EDTA buffer: a formulation of 10 mM Tris-HCL, 1 mM disodium EDTA buffer, pH 8. Sodium citrate buffer: a formulation of 0.01 M sodium citrate, with 0.01 M citric acid, pH 6.0. Pepsin solution, pH 2.0.

Antibody	Clone	Primary antibody type	Host	Localization	Dilutions	Retrieval buffer	Source
GCDFP-15	D6	IgG2a monoclonal	Mouse	Cytoplasmic	1:100	Pepsin solution	Biocare Medical, Pacheco, CA, USA
p63	DAK-P63	IgG2a monoclonal	Mouse	Nuclear	1:200	Tris-EDTA	DAKO, Santa Clara, CA, USA
SMA	1A4	IgG2a monoclonal	Mouse	Cytoplasmic	1:100	Sodium citrate	Thermo Fischer Scientific, Waltham, MA, USA

Table 2 | Clinical characteristics of 11 tumors diagnosed as apocrine hidrocystomas.

Case	Sex	Age	Localization	Number	Length (mm)	Width (mm)
A1	Male	54	Eyebrow	Solitary	17	9
A2	Female	37	Neck	Solitary	8	5
A3	Female	65	Eyelid	Solitary	12	9
A4	Female	36	Left upper eyelid	Solitary	6	2
A5	Male	55	Eyelid	Solitary	23	8
A6	Male	75	Eyelid	Solitary	12	7
A7	Male	55	Eyelid	Solitary	3	4
A8	Male	86	Tip of nose	Solitary	24	22
A9	Female	53	Right eyelid	Multiple	6	4
A10			Right ear	Multiple	10	6
A11	Female	61	Left eyelid	Solitary	9	5

Table 3 | Clinical characteristics of 11 tumors diagnosed as eccrine hidrocystomas.

Case	Sex	Age	Localization	Number	Length (mm)	Width (mm)
E1	Male	45	Eyelid	Solitary	5	4
E2	Female	78	Eyelid	Solitary	8	4
E3	Female	46	Inner canthus	Solitary	4	3
E4	Male	55	Eyelid	Solitary	7	5
E5	Male	52	Left upper eyelid	Multiple	15	6
E6			Left lower eyelid	Multiple	7	4
E7	Male	27	Eyelid	Solitary	15	3
E8	Female	53	Eyelid	Solitary	6	5
E9	Male	49	Eyelid	Solitary	6	4
E10	Female	71	Eyelid	Solitary	4	2
E11	Female	60	Inner canthus	Solitary	3	2

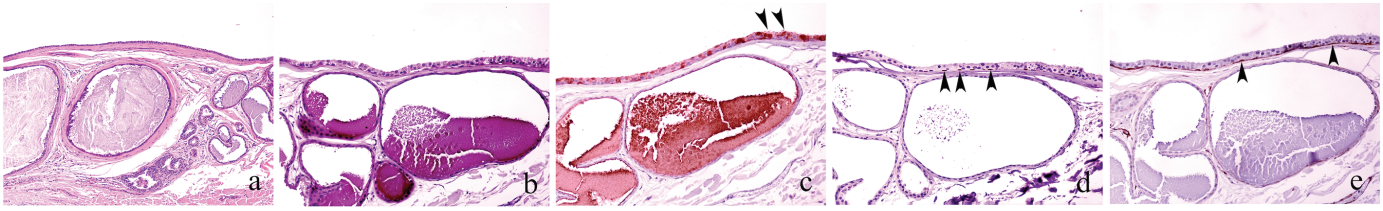

Figure 1 | (a) Hematoxylin and eosin (H/E) stain shows a multilocular cyst in the dermis characterized by an inner lining of large columnar cells showing luminal "decapitation" secretion indicative of apocrine secretory activity and an outer lining of elongated myoepithelial cells with their long axes running parallel to the cyst wall; (b) periodic acid–Schiff (PAS) staining demonstrates the presence of PAS-positive granules in the secretory cells; (c) the apocrine nature of the secretory cells (arrowheads) is shown by positivity in the GCDFP-15 stain; (d) p63 and (e) SMA staining highlight the peripherally located row of myoepithelial cells (arrowheads); (a: magnification 100×, b–e: magnification 200×).

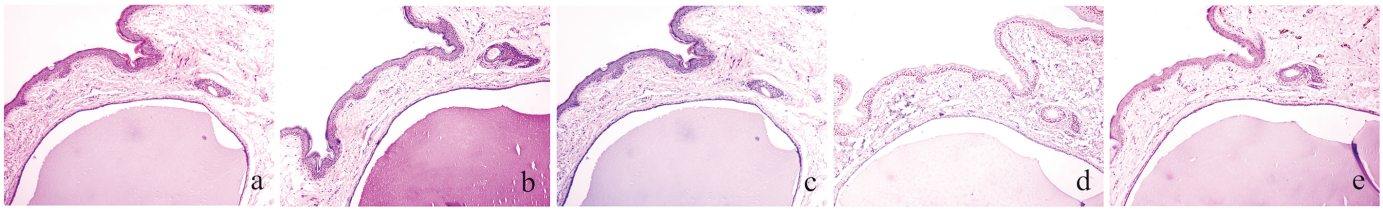

Figure 2 | (a) Hematoxylin and eosin (H/E) shows a unilocular dermal cyst in the vicinity of the epidermis lined by two layers of small cuboidal epithelial cells with eosinophilic cytoplasm with no evidence of decapitation secretion, similar to the epithelial cells lining eccrine gland ducts, and containing pale eosinophilic secretions; (b) periodic acid–Schiff staining and (c) GCDFP-15 staining were negative. An outer layer of myoepithelial cells is not present, as evidenced by (d) negative staining with p63 and (e) SMA; (a: magnification 100×, b–e: magnification 200×).

Aulus Cornelius Celsus is credited with the first description of *hidrocystoma* under the term *hydatis* (12). Later, the term was also used by Soranus of Ephesus and Galen (1st to 2nd century AD) and eminent Byzantine physicians, such as Oribasius (4th century), Aetios of Amida (6th century), Alexander Trallianos (6th century), Paul of Aegina (7th century), and Theophilus Protospatharius (7th century). In English medical literature, Robinson first introduced the term *hydrocystoma* to refer to watery cysts on the face (13–15). In his book *The Histological Pathology of Diseases of the Skin*, published in 1896, Unna defines hydrocystoma as "a multiple appearance of large duct cysts accompanying by excessive hydrosis" (16). In the pathology book by Cheng and Bostwick, the term *hydrocystoma* is also used, referring to "water cysts" (17). The term was finally changed to *hidrocystoma* (from Greek *hidros* 'sweat'), referring to cysts on the face originating from the apocrine sweat glands. Other terms have also been proposed (e.g., *Robinson's disease or sudoriferous cysts*), but they caused more confusion than clarity and did not gain wide acceptance.

Here we present a relatively large case series of hidrocystomas in Greece and one of the largest series compared to current literature. Hidrocystomas usually affect adults with the same prevalence between males and females (4), as in our study. However, other studies report larger female:male ratios, up to 2:1 (9). Mean age ranges from 30 to 70 years (4). Maeng et al., report a mean age of 56 years in their large cohort (9), exactly as in our study. However, pediatric patients with orbital lesions have also been reported (18). In our cohort, eccrine and apocrine hidrocystomas were equally frequent (50%), although other studies indicate the former as rarer, counting for approximately 22% of all lesions, and the latter as more commonly misdiagnosed (19).

In apocrine hidrocystomas, apocrine decapitation secretion may be present. Apocrine hidrocystomas are more likely to be a neoplasm and they are often multiloculated. Eccrine hidrocystomas are more likely to be a unilocular retention of sweat in a dilated duct or gland rather than a cystic neoplasm. There is no decapitation secretion. Histology confirms the diagnosis of hidrocystomas. Only apocrine hidrocystomas, and not eccrine hidrocystomas, stain positive for GCDFP-15, p63, and aplha-SMA (2–5). The stain PAS is positive for apocrine hidrocystomas and negative for eccrine hidrocystomas (20), as in our study. In eccrine hidrocystomas there are no secretory cells and no decapitation of cells, but there is decapitation of secretory cells in apocrine hidrocystomas (20). Alpha-SMA-, CK7-, and/or GCDFP-15–positive apocrine hidrocystomas have been reported to arise from glandular secretory spirals within the marginal, perimarginal, or canthal skin. Absent alpha-SMA suggests an eccrine ductal origin, whereas CK7 positivity characterizes the apocrine secretory spiral but not ducts (19).

The gold standard of treatment is surgical excision, with potential complications including ectropion, which can cause epiphora, lagophthalmos, keratinization, chronic irritation, pain, and ulceration (8). Other treatment modalities that have also been used, including CO2 laser, pulse dye laser (PDL), cryotherapy, electrosurgery, diode and argon laser, botulinum toxin injection, topical ipratropium, glycopyrrolate, atropine, and aluminum chloride (8).

Limitations of our study include its retrospective and single-center nature, and the small number of patients. To the authors' knowledge, this is the first large case series of hidrocystomas from Europe and the Mediterranean region describing clinical and histopathological characteristics of this rare entity.

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