

Vulvar Hidradenoma Papilliferum

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Aim: This study examines the clinical and pathological characteristics, immune profile, histological occurrence, diagnosis, and differential diagnosis of vulvar hidradenoma papilliferum.

Methods: An analysis was conducted on clinical data, histological patterns, and immunohistochemical findings from 45 cases of vulvar hidradenoma papilliferum, and relevant published articles were reviewed. Simultaneously, high-risk HPV typing was performed on these 45 cases.

Results: The 45 cases of vulvar hidradenoma papilliferum displayed tumor sizes ranging from 0.3 to 2.0 cm and were observed to be pink or red in appearance. Vacuolated cytoplasm, large abnormal nuclei, distinct nucleoli, and scattered eosinophilic luminal secretions were observed in the glands. Positive staining for CK7 and progesterone receptor (PR) with focal mammaglobin and GCDFP-15 expression was found through immunohistochemistry. CK20 staining was noted as negative.

Conclusion: Hidradenoma papilliferum is a rare benign tumor that originates in secretory glands. The diagnosis of this condition is aided by gross and immunohistochemical results, and differentiation from other conditions is necessary.

Keywords: differential diagnosis, immunohistochemical staining, vulvar hidradenoma papilliferum

Introduction

Hidradenoma papilliferum is a rare benign tumor that occurs in the skin, primarily affecting women during their reproductive years. It is most commonly found in the vulva, perianal area, and perineum but can occasionally occur in the nipples, eyelids, and external auditory canal. This tumor involves the anal mammary glands and shares morphological similarities with intraductal papillomas of the breast.¹⁻⁶ To date, the literature contains very few reported cases, and English and Chinese reports are typically based on individual cases. In this study, we collected 45 cases and conducted a literature review to analyze their pathology and clinical characteristics, aiming to enhance understanding of the disease among pathologists and clinicians.

Methods

The study included 45 cases from Jinhu County People's Hospital in Jiangsu Province, Dazhou People's Hospital in Sichuan Province, First People's Hospital of Zigong City in Sichuan Province, and Suining City People's Hospital in Sichuan Province, spanning from January 2014 to March 2021. These specimens were fixed in 10% neutral formalin, followed by paraffin block preparation and subsequent hematoxylin and eosin staining. Immunohistochemical staining was conducted using the streptavidin-biotin method with a Lab Vision Secondary Detection Kit. In brief, the sections underwent a 20-minute deparaffinization step to block endogenous peroxidase activity. Antigen retrieval was performed with citrate buffer at pH 6.0 before antibody incubation. Subsequently, the slides were incubated with ER, PR, AR, CK7, CK20, P63, CK5/6, and Ki67 antibodies, all of which were procured from China's Fujian Maixin Technology Company. 3,3'-Diaminobenzidine was employed as the chromogen. Finally, the sections were counterstained with hematoxylin solution for 1 minute and then mounted for microscopic observation.

Results

The age range of the patients was 24 to 75 years, with an average age of 47 years. Among the patients, there were 6 pregnant women (6/45, 13.33%). Tumor diameters ranged from 0.3 to 2.0 cm, with 34 cases occurring in the vulva (34/45, 75.46%), 2 cases in the perineum (2/45, 4.44%), 3 cases in the hymen (3/45, 6.67%), and 6 cases in the labia majora (6/45, 13.33%) (Table 1). Microscopic observations revealed the following features: The tumor was located in the dermis with clear borders and a solid cystic appearance. There was noticeable fibrous tissue proliferation surrounding the tumor. The tumor consisted of acinar structures, glandular ducts, and complex folded papillary structures of varying sizes, resulting in a complex appearance. The central portion of the tumor resembled typical mammary ducts, containing narrow and thin fibrovascular stroma that separated the glands within it. The glandular lumens and papillary structures were lined with a single layer of columnar epithelial cells, with evident apocrine secretion in some areas. The nuclei of the cells were large, lightly stained, oval, located at the base, and exhibited weakly eosinophilic cytoplasm. Spindle-shaped or cuboidal myoepithelial cells were observed at the periphery of the columnar cells, with small, round or oval nuclei and hyperchromatic, partially transparent cytoplasm. They formed a double-layer arrangement with the inner columnar cells. Neither the columnar epithelial cells nor the myoepithelial cells displayed significant atypia, and no atypical mitoses or necrosis were detected in any of the tumors (Figure 1A–D). Immunohistochemical staining results indicated the following: All tumors exhibited expression of ER by the inner columnar cells (Figure 2A). PR expression was observed in the inner columnar cells of all tumors (Figure 2B). AR was expressed by the inner columnar cells (Figure 2C). CK7 expression was present in the inner columnar cells (Figure 2D). P63 and S-100 were expressed by all tumor myoepithelial cells (Figure 2E and 2F). Local expression of GCDFP-15 was observed. All 45 cases expressed 34βE12 (Figure 2G), but CK20 expression was absent (Figure 2H). The Ki67 proliferation index ranged from approximately 2% to 10%.

Discussion

In 1878, Worth first identified hidradenoma papilliferum as small, harmless growths that originate in the sweat gland secretions of middle-aged women, typically aged 30 to 49 years.⁷ These growths develop slowly and can persist for an extended period. They commonly appear as rounded, firm, and slightly raised lumps under the skin with well-defined borders. They are often painless but can occasionally cause discomfort and irritation. These growths typically range in size from 0.1 to 1.0 cm in diameter, with rare cases exceeding 2.0 cm.⁸ In our report of 45 cases, the median age of patients was 47 years, and the size of the growths ranged from 0.3 to 2.0 cm, consistent with findings in existing literature.

Table 1 Clinical Data of 45 Cases of Vulvar Hidradenoma Papilliferum

Characteristic	Value
Mean age	47
Pregnancy woman	6
Size	
≤0.5	7
>0.5	38
Location	
Vulvar	34
Perineum	2
Hymen	3
Labia majora	6
Mitotic count	
≤5	41
>5	4
Follow up (96–12 months)	No recurrence

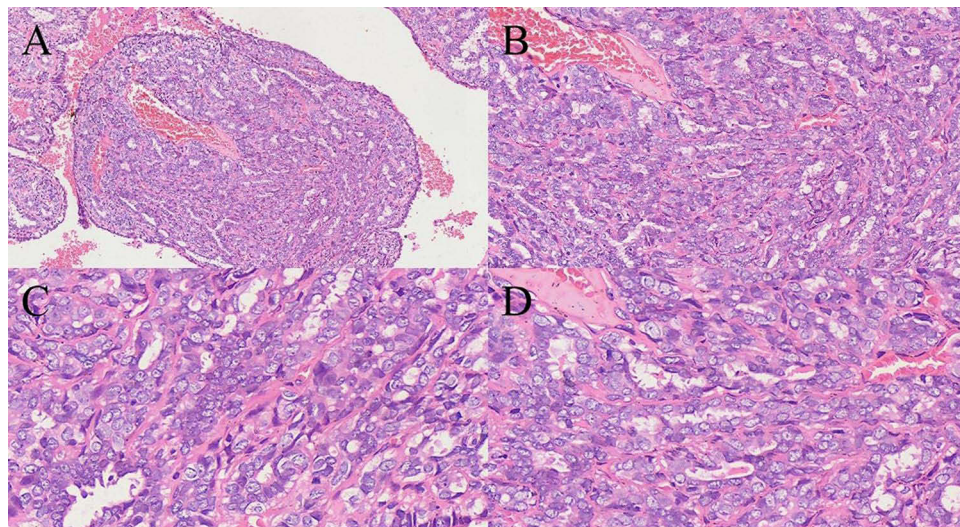


Figure 1 Histopathological Images (A–D) Show tumor composed of irregular glandular structures arranged in a labyrinth pattern, characteristic of hidradenoma papilliferum (Hematoxylin and eosin).

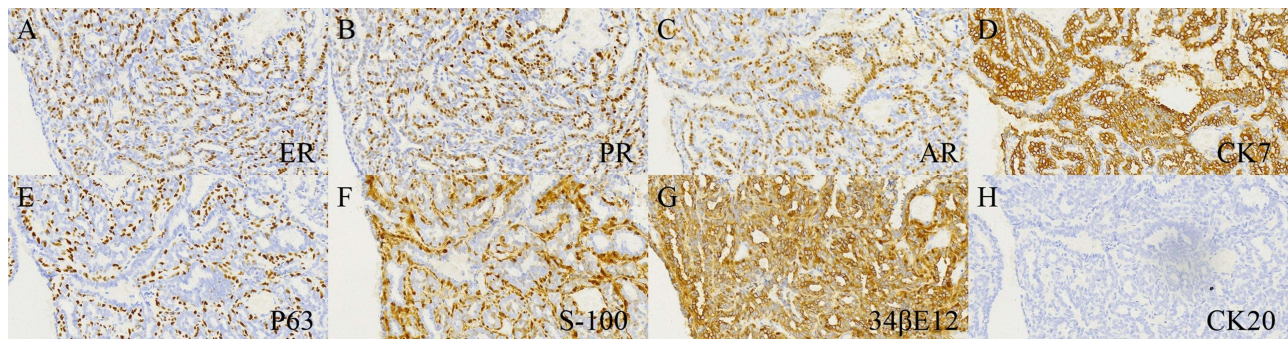


Figure 2 (A–G) Demonstrating tumor cells positive for ER, PR, AR (androgen receptor), CK7, P63, S100, and 34βE12. (H) Indicates tumor cells negative for CK20.

The tumor is situated in a small portion of the subcutaneous layer just beneath the skin's surface. It exhibits characteristics of both cystic and solid structures, displaying well-defined boundaries and being surrounded by fibrous connective tissue. Importantly, it is not connected to the epidermis, which is the outermost layer of the skin. The tumor consists of various-sized acinar structures, glandular ducts, and intricately folded papillary formations, resulting in a complex appearance. The gland cavities and papillary structures are lined with a single layer of columnar epithelial cells, and in some areas of the cavities, clear apocrine secretion is visible. Myoepithelial cells are present outside the columnar cells, creating a distinctive double-layered structure with the inner columnar cells. It's worth noting that both the columnar epithelial cells and myoepithelial cells in this bilayered epithelium exhibit no atypical characteristics, such as atypical mitotic figures or necrosis. Additionally, they can differentiate into apocrine and sebaceous glands.

In terms of immunophenotype, most papillary hidradenomas typically show expression of ER, PR, CK7, and EMA. Furthermore, the myoepithelial cells within the tumor express P63, S100, and CD10, consistent with the findings reported by Nishine et al.⁹ However, in some of our cases, GCDPF15 is expressed due to the presence of differentiated apocrine glands within the tumor.

Vulvar hidradenoma papilliferum must be distinguished from several other conditions: Papillary adenocarcinoma: When Vulvar hidradenoma papilliferum grows larger and develops ulceration, it can protrude above the skin's surface as a dark red papilla, which may be mistakenly diagnosed as cancer in a clinical setting. Papillary adenocarcinoma lacks encapsulation and has unclear boundaries with the surrounding tissue. It exhibits prominent cell atypia, frequent presence of atypical mitotic

figures, and necrosis. The growth pattern is irregular and invasive. However, unlike hidradenoma papilliferum, it lacks apocrine secretion and a double-layered structure.^{10,11} Syringocystadenoma papilliferum: Both hidradenoma papilliferum and syringocystadenoma papilliferum originate from apocrine glands and may exhibit similar histopathological features. Syringocystadenoma papilliferum is characterized by cystic invaginations extending downward from the epidermis in a papillomatous pattern. These cystic depressions are connected to the epidermis and lined with double-layered epithelial cells. The papillary interstitium is thick, dilated capillaries and numerous plasma cells are observed, and dilated apocrine glands are often present beneath the tumor mass. Additionally, syringocystadenoma papilliferum is more commonly found on the head and face, slightly more prevalent in men than women, and it opens in the epidermis and connects with it, which distinguishes it from Vulvar hidradenoma papilliferum.³ Papillary syringoma: This condition is more frequently seen in young women and tends to be multiple and bilaterally symmetrical, often occurring in the labia. Papillary syringoma tumors are generally small, ranging from 0.1 to 0.4 cm in diameter, and have a firm texture. Unlike hidradenoma papilliferum, papillary syringoma arises from sweat glands differentiated from eccrine ducts and is often associated with endocrine factors and pregnancy. The tumor is situated in the superficial layer of the dermis, primarily composed of epithelial cells and fibrous stroma. Within the fibrous stroma, numerous small ducts are visible, forming clusters of tubular epithelial cells with a comma-shaped appearance. These clusters are scattered throughout and lack features such as apocrine secretion and a double-layered structure. Extramammary Paget disease: This condition is more prevalent in women beyond middle age, typically affecting the labia majora, perineum, or perianal region. It is often accompanied by persistent pain and itching and exhibits a prolonged pre-infiltration stage. Clinically, it presents as a multifocal, well-defined eczema-like plaque. Microscopically, characteristic Paget cells are found scattered or arranged in glandular tubes within the epidermis and skin appendages. These cells stain positively for mucus and commonly express CK7 and CEA. In clinical practice, hidradenoma papilliferum is sometimes misdiagnosed as polyps, external hemorrhoids, powder tumors, or viral warts.¹² It's essential to note that hidradenoma papilliferum is a benign tumor, and the preferred treatment is complete surgical resection. Recurrence and malignant transformation are rare, with very few recurrence cases resulting from incomplete resection. Some researchers suggest that HPV (human papillomavirus) may play a role in the carcinogenesis of hidradenoma papilliferum. Furthermore, mutations in cancer-related genes like PIK3CA, AKT1, BRAF, APC, and ERBB4 have been identified in hidradenoma papilliferum patients, raising the possibility of malignant transformation.¹³ While some tumors may exhibit an increased number of mitotic figures, the clinical prognosis of hidradenoma papilliferum cannot be predicted solely based on mitotic counts. Consideration of malignant transformation should only arise when atypical mitoses and necrosis are present.¹⁴ However, it's important to note that although this study included 45 cases, there is a lack of research evidence regarding genetic alterations.

Conclusions

In conclusion, when adult women exhibit nodular lesions in the vulvar region, it is crucial to distinguish these from sexually transmitted diseases and other both benign and malignant vulvar conditions. The patient's medical history and clinical presentation alone may not provide a definitive diagnosis of papillary sweat glands. Therefore, surgical removal of the lesion and subsequent histopathological assessment are essential steps to establish a definitive diagnosis.

Ethical Approval

The studies involving human participants were reviewed and approved by the Institutional Ethical Committee of the Jinhu County People's Hospital (ethical review number: JHRY: NO.2021-025). The patients/participants provided their written informed consent to participate in this study. The present study fulfils the requirements of the Declaration of Helsinki.

Acknowledgments

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Author Contributions

The author made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors affirm that they have no conflicts of interest to disclose for this work.

References

1. van der Putte SC. Mammary-like glands of the vulva and their disorders. *Int J Gynecol Pathol*. 1994;13:150–160. doi:10.1097/00004347-199404000-00009
2. Moon JW, Na CH, Kim HR, Shin BS. Giant ectopic hidradenoma papilliferum of the scalp. *J Dermatol*. 2009;36:545–547. doi:10.1111/j.1346-8138.2009.00697.x
3. Minami S, Sadanobu N, Ito T, et al. Non-anogenital (ectopic)hidradenoma papilliferum with sebaceous differentiation: a case report and review of reported cases. *J Dermatol*. 2006;33:256–259. doi:10.1111/j.1346-8138.2006.00062.x
4. Vang R, Cohen PR. Ectopic hidradenoma papilliferum: a case report and review of the literature. *J Am Acad Dermatol*. 1999;41:115–118. doi:10.1016/S0190-9622(99)70418-4
5. Jain D, Siraj F, Grover AK, et al. Hidradenoma papilliferum presenting as an eyelid mass. *Ophthal Plast Reconstr Surg*. 2012;28(6):e152–153. doi:10.1097/IOP.0b013e31825238ae
6. Tanaka M, Shimizu S. Hidradenoma papilliferum occurring on the chest of a man. *J Am Acad Dermatol*. 2003;48(2 Suppl):S20–21. doi:10.1067/mjd.2003.125
7. Baker GM, Selim MA, Hoang MP. Vulvar adnexal lesions: a 32-year, single institution review from Massachusetts general hospital. *Arch Pathol Lab Med*. 2013;2013(137):1237–1246. doi:10.5858/arpa.2012-0434-OA
8. Kazakov DV, Mikyskova I, Kutzner H, et al. Hidradenoma papilliferum with oxyphilic metaplasia: a clinicopathological study of 18 cases, including detection of human papillomavirus. *Am J Dermatopathol*. 2005;27(2):102–110.
9. Nishie W, Sawarura D, Mayuzumi M, et al. Hidradenoma papilliferum with mixed histopathologic features of syringocystadenoma papilliferum and anogenital mammary-like gland. *J Cutan Pathol*. 2004;31(8):561–564. doi:10.1111/j.0303-6987.2004.00176.x
10. Milliken S, May J, Sanderson PA, et al. Reducing the radicality of surgery for vulvar cancer: are smaller margins safer? *Minerva Obstet Gynecol*. 2021;73(2):160–165. doi:10.23736/S2724-606X.20.04743-7
11. Giannini A, D'Oria O, Chiofalo B, et al. The giant steps in surgical downsizing toward a personalized treatment of vulvar cancer. *J Obstet Gynaecol Res*. 2022;48(3):533–540. doi:10.1111/jog.15103
12. Daniel F, Mahmoudi A, de Parades V, et al. An uncommon perianal nodule: hidradenoma papilliferum. *Gastroenterol Clin Biol*. 2007;31(2):166–168. doi:10.1016/S0399-8320(07)89349-3
13. Pfarr N, Sinn HP, Klauschen F, et al. Mutations in genes encoding PI3K-AKT and MAPK signaling define anogenital papillary hidradenoma. *Genes Chromosomes Cancer*. 2016;55(2):113–119. doi:10.1002/gcc.22315
14. Sington J, Chandrapala R, Manek S, et al. Mitotic count is not predictive of clinical behavior in hidradenoma papilliferum of the vulva: a clinicopathologic study of 19 cases. *Am J Dermatopathol*. 2006;28(4):322–326. doi:10.1097/00000372-200608000-00005

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