Papillary Cystadenoma of the Epididymis

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- Papillary cystadenoma is a rare benign neoplasm of the epididymis, occurring mainly in young adult males. More than one-third of the cases reported in the literature have occurred in patients with von Hippel-Lindau disease. Conversely, epididymal nodules presumed to be papillary cystadenomas are found in one-third of males with von Hippel-Lindau disease. The association is stronger for bilateral tumors. The pathogenesis involves loss of the von Hippel-Lindau gene resulting in overexpression of the angiogenic protein “hypoxia-inducible factor.” Papillary cystadenoma is of mesonephric derivation. It originates in the efferent ductules of the head of the epididymis in the form of tiny precursor lesions. Histologically, papillary cystadenoma is characterized by cystic spaces with intracyctic papillary projections lined by clear cells, with a resultant resemblance to renal cell carcinoma. Immuno-histochemical markers may facilitate the distinction between the 2 tumors. Treatment consists of surgical excision and the prognosis is excellent.

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Neoplasms of the epididymis are rare. Benign epididymal neoplasms include adenomatoid tumor (most common), leiomyoma, serous (nonpapillary) cystadenoma, cavernous hemangioma, and melanotic neuroectodermal tumor. Malignant tumors involving the epididymis include adenocarcinoma, mesothelioma, and metastatic renal cell carcinoma.

Papillary cystadenoma is a rare benign epithelial tumor of the epididymis. Only 59 histologically documented cases have been reported in the English-language literature since the original report by Sherrick in 1956. The history of this tumor goes back to 1921, when Brandt found an “epididymal cyst” in an autopsy of a patient for which von Hippel had previously reported retinal lesions. Slides from this case were subsequently reviewed by Lindau, who noted that the tumor was “hypernephroid.” The largest series in the literature is a study of 20 patients (including 17 new cases) from the Armed Forces Institute of Pathology reported by Price in 1971. In this article, we review and discuss the clinical and pathologic features of papillary cystadenoma of the epididymis (PCE) that are based on a detailed analysis of histologically documented cases reported in the literature.

**CLINICAL FEATURES**

The clinical features are summarized in Table 1. Most cases of PCE occur in young adults, but patients may range in age from 16 to 76 years (mean, 35 years; median, 30 years). Papillary cystadenoma of the epididymis is often discovered incidentally. Of the incidentally detected cases, some are found during examination of patients for other reasons, including von Hippel-Lindau disease (VHLD), while others are detected at autopsy. Among symptomatic patients, the most common presentation is a painless, slowly growing scrotal swelling. A small number of patients present with pain or tenderness in the scrotum or are found to have an epididymal nodule during workup for infertility.

Papillary cystadenoma of the epididymis may involve 1 epididymis or both epididymides. Unilateral cases are more common and in most of these, no other stigmata of VHLD are detectable. A small but significant proportion of unilateral PCE occurs in association with VHLD. In all 8 reported cases of this occurrence, PCE was discovered in patients with an established diagnosis of VHLD. To the best of our knowledge, unilateral PCE has never been reported as the initial presentation of VHLD. Bilateral PCE occurs mostly in patients with previously diagnosed VHLD, but in some cases there is no evidence of other stigmata of the disease. Analysis of the 59 cases reported in the literature thus far shows that bilateral PCE is significantly more likely to be associated with VHLD than unilateral PCE ($P = .001$; 2-tailed Fisher exact test).

The association of PCE with VHLD is its most interesting and significant feature. The precise relationship is difficult to quantify for 2 reasons. First, most cases of PCE reported in large series of VHLD lack histologic documentation. Second, the tumor often does not cause symptoms and may easily escape detection unless a specific effort is made to examine the patient for epididymal nodules. Therefore, the highly variable reported incidence of PCE in VHLD is a function of the diligence with which the tumor was specifically sought. Melmon and Rosen found epididymal cysts or nodules in 6 of 9 male patients (66%) with VHLD. In contrast, Lamiell et al found epididymal masses by examination in 7 of 22 males (32%) with VHLD. In the same paper, however, a review of the incidence reported by others yielded an even lower figure (17%), perhaps because the tumor was not specifically sought in those reports. Finally, more recent studies carried out by using extensive histologic sampling have found PCE or its precursors in...
Table 1. Clinical Features of 59 Reported Cases of Papillary Cystadenoma of the Epididymis

<table>
<thead>
<tr>
<th>Age (information known for 59 cases), y</th>
<th>Range</th>
<th>Mean</th>
<th>Median</th>
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<td>16–76</td>
<td>35</td>
<td>30</td>
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- Clinical presentation (information known for 54 cases), No. (%)
  - Swelling or mass: 21 (39)
  - Incidental finding: 20 (37)
  - Intertubility: 8 (15)
  - Pain: 5 (9)

- Laterality (information known for 59 cases)
  - Unilateral, No. (%): 35 (59)
  - Bilateral, No. (%): 24 (41)
  - VHLD: 8

- Association with VHLD (information known for 59 cases), No. (%)
  - VHLD: 24 (40)
  - No evidence of VHLD: 35 (60)

Abbreviation: VHLD, von Hippel-Lindau disease.
* Analysis includes all cases in the English-language literature in which the diagnosis was confirmed histologically.

Table 2. Pathologic Findings in 59 Reported Cases of Papillary Cystadenoma of the Epididymis

<table>
<thead>
<tr>
<th>Diagnostic procedure (information known for 56 cases), No. (%)</th>
<th>Excision</th>
<th>44 (78)</th>
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<tbody>
<tr>
<td></td>
<td>Biopsy</td>
<td>6 (11)</td>
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<td></td>
<td>Autopsy</td>
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- Size of lesion (information known for 46 cases)*, cm
  - Range: 0.5–8
  - Mean: 2.1
  - Median: 2

- Clear cells (information known for 55 cases), No. (%)
  - Present: 52 (95)
  - Absent: 3 (5)

- Immunohistochemical markers, (positive/total cases tested)
  - Epithelial membrane antigen: 9/9
  - Keratin AE1/AE3: 7/7
  - CK7: 5/5
  - CAM 5.2: 3/3
  - Panckytoheratin: 2/2
  - PAX2: 1/1
  - CD10: 0/5
  - CK20: 0/4

- Discordant results
  - Vimentin: 3/6
  - CEA: 2/4
  - Renal cell carcinoma marker: 1/3
  - S100: 1/4

Abbreviations: CEA, carcinoembryonic antigen; CK, cytokeratin.
* In bilateral tumors for which the size of both tumors was documented, both tumors were included in the analysis.

Histologically, PCE is characterized by cysts filled with prominent intracytoplasmic papillary projections (Figure 1, B). The papillae contain fibrivascular cores and are lined by a single layer of bland cuboidal or columnar epithelium. The cells are also commonly arranged in tubules or nests. Cell borders are prominent. Cilia are occasionally present. Cytoplasmic clearing is a conspicuous feature (Figure 1, C), present in almost all reported cases (Table 2). It is related to the presence of intracytoplasmic glycogen or fat. The resultant resemblance to clear cell renal cell carcinoma (RCC) can be striking. In most cases, the cysts are filled with an eosinophilic, colloid-like material. The supporting stroma may be vascular, collagenous, or inflamed. Nuclear atypia, stratification, mitoses, necrosis, psammoma bodies, and invasion of surrounding structures are absent.

Immunohistochemically, the epithelial cells of PCE are consistently positive for cytokeratin AE1/AE3, CAM 5.2, and epithelial membrane antigen (EMA). The keratin profile is CK7 positive (Figure 1, D) and CK20 negative. The renal cell carcinoma marker, PAX2, is variably positive. PAX2 has been reported to be positive in 1 case. CD10 has been negative in all cases tested. Positivity for CK7 and negativity for CD10 were recently successfully used to demonstrate a rare case of a tumor-to-tumor metastasis from a clear cell RCC to a PCE.

**PATHOGENESIS AND MOLECULAR/GENETIC FINDINGS**

In 1995, the cells of some sporadic PCEs were shown to harbor somatic VHLD gene mutations. Three years later, Leung et al reported high levels of vascular endothelial...
growth factor messenger RNA in the epithelial cells of PCE in a patient with VHLD. They postulated that elevated levels of vascular endothelial growth factor contributes to new vessel formation, increased vascular permeability, fluid accumulation, and cyst formation.

Our understanding of the pathogenesis of PCE has been greatly enhanced by 2 recent studies of epididymides from patients with VHLD. These elegant studies have demonstrated the presence of precursor lesions confined to the efferent ductules of the head of the epididymis. Since the epididymis, like the kidney, is of mesonephric origin, these findings suggest that PCE is of mesonephric derivation and that maldeveloped mesonephric material may play a role in the pathogenesis of VHLD-associated tumors. The tiny precursor lesions in these studies were shown to be morphologically, immunohistochemically, and genetically identical to PCE. Another key finding that emerged from these studies was the role of VHLD gene loss, with resultant activation of the angiogenic protein ‘hypoxia inducible factor.’"

**DIFFERENTIAL DIAGNOSIS**

The most important lesion in the differential diagnosis of PCE is metastatic clear cell RCC. Features common to the 2 lesions include cystic, tubular, and nested architecture; prominent vascular stroma; and clear cells. Both may occur in patients with VHLD. The mean age (37 years) of patients with renal cell carcinoma in VHLD is similar to the mean age of occurrence of PCE (35 years, our analysis). A CK7-positive, CD10-negative profile has been shown to differentiate PCE from metastatic RCC. The value of CK7 and CD10 in this differential diagnosis has also been recently demonstrated in documenting a tumor-to-tumor metastasis of a clear cell RCC to a PCE. However, discordant results were reported in another study in which a single case of PCE tested positive for PAX2 and RCC marker. It must be stressed that CD10 and RCC marker are simply markers of proximal tubule differentiation and are not specific for RCC. Reported positivity for these markers in clear cell RCC varies from 82% to 94% for CD10 and 47% to 85% for RCC marker. Therefore, CD10 and RCC marker positivity must be interpreted in the context of the overall morphologic features. The role of ultrastructural examination in the differential diagnosis between PCE and clear cell RCC remains to be elucidated. The reported ultrastructural features of PCE include the presence of microvilli, lacy cytoplasm, and abundant tonofibrils. To the best of our knowledge, these findings...
have not been compared to those of clear cell RCCs. Serous adenocarcinoma of the paratestis is distinguished from PCE by the presence of nuclear atypia and invasive growth. Papillary cystadenoma of the epididymis must also be distinguished from paratesticular papillary mesothelioma, which can involve the epididymis, has papillae, and is positive for epithelial markers. Features that distinguish papillary mesothelioma from PCE include the absence of clear cells and the presence of calretinin positivity. Another epithelial lesion with papillary architecture is serous borderline tumor of the paratestis.

This lesion can be differentiated from PCE by the absence of clear cells, the presence of a stratified lining, and the occasional presence of psammoma bodies. Papillary cystadenoma of the epididymis is easily differentiated from the recently described serous (nonpapillary) cystadenoma of the epididymis by the lack of papillary architecture in the former.

**TREATMENT AND PROGNOSIS**

Treatment of PCE consists of testicle-sparing surgical excision. Local excision is usually feasible, although some patients do undergo orchectomy. It has been suggested that patients be followed after excision. There is 1 report of recurrence (possibly due to incomplete initial excision) and 2 reports of transformation to cystadenocarcinoma. The possibility of VHLD should be considered in all patients with PCE, since they may be at risk of developing other VHLD-associated tumors. For reasons discussed previously, radiologic or genetic testing for VHLD is probably warranted only in patients with bilateral PCE.

**SUMMARY**

Papillary cystadenoma of the epididymis is a rare benign neoplasm of the epididymis, remarkable for its frequent association with VHLD and its morphologic similarity to clear cell RCC. Although immunohistochemistry has been shown to be useful in the differential diagnosis of these 2 tumors, some markers hitherto considered specific for RCC may be expressed in PCE. Our understanding of the pathogenesis of PCE in VHLD has been enhanced by 2 recent reports demonstrating that, in patients with VHLD, PCE arises in the effferent ductules of the head of the epididymis, is of mesonephric origin, and is preceded by morphologically, immunohistochemically, and genetically similar precursor lesions.

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**References**