Int J Clin Exp Pathol 2026;19(6):261-266
www.ijcep.com /ISSN:1936-2625/IJCEP0172275

Case Report

A rare case of multiple papillary cystadenomas found in a female patient with von Hippel-Lindau syndrome

Haruka Hatakeyama[1], Ikumi Shioya[1], Yohei Kawasaki[1,2], Maya Suzuki[1], Masahito Miura[1], Yuko Hiroshima[3], Hiroshi Nanjo[3], Yasufumi Omori[1]

[1]Department of Molecular and Tumour Pathology, Akita University Graduate School of Medicine, Akita, Japan; [2]Department of Otorhinolaryngology and Head-and-Neck Surgery, Akita University Graduate School of Medicine, Akita, Japan; [3]Division of Clinical Pathology, Akita University Hospital, Akita, Japan

Received February 25, 2026; Accepted May 6, 2026; Epub June 15, 2026; Published June 30, 2026

Abstract: Papillary cystadenoma (PC) is a benign epithelial tumor believed to be of mesonephric origin and is recognized as one of von Hippel-Lindau syndrome (VHL)-related neoplasms. PC tends to develop frequently in male VHL patients but rarely in females and arises from the mesosalpinx or broad ligament in females. Having experienced a case of multiple PCs in a female patient, we here report it with literature review. The patient was a 34-year-old woman. In her past medical history, VHL including multiple hemangioblastomas of the central nervous system, pancreatic neuroendocrine tumor, and multiple clear cell renal cell carcinoma (CCRCC) of the bilateral kidneys was diagnosed. In addition, a PC of the left ovary was resected seven years earlier. In the present report, she was admitted to our hospital because of lower abdominal pain, and then computed tomography revealed swelling of the right ovary and ascites. She was diagnosed with right ovarian torsion and thus salpingo-oophorectomy was performed. Histopathologically, while the tumor cells with pale or eosinophilic cytoplasm showed a papillary growth with partial cystic changes, none of apparent nuclear atypia, mitotic figure, and necrosis were observed. We finally diagnosed it as PC of the right ovary. Its pathological findings were similar to those of the previously resected left ovarian lesion. Although PC is rare in females, the presence of VHL should be kept in mind when PC is encountered. Moreover, metastatic CCRCC should also be considered to be one of differential diagnoses in VHL patients.

Keywords: Papillary cystadenoma, von Hippel-Lindau syndrome, immunohistochemistry

Introduction

Papillary cystadenoma (PC) is a benign epithelial neoplasm recognized as a characteristic manifestation of von Hippel-Lindau syndrome (VHL). VHL is a rare genetic disorder characterized by the growth of tumors and cysts in various parts of the body. It is caused by mutations in the VHL tumor suppressor gene on chromosome 3 and typically follows an autosomal dominant inheritance pattern. Affected individuals are prone to developing hemangioblastomas in the brain and retina, clear cell renal cell carcinomas, pheochromocytomas, and PC [1]. Because these tumors can affect multiple organs, including the kidneys, pancreas, and adrenal glands, regular screening and multidisciplinary care are essential for early detection and management to prevent serious complications. PC is a rare, benign epithelial tumor that occurs in the reproductive tract of individuals with VHL. In men, it typically develops in the epididymis, while in women, it appears in the broad ligament. These tumors are highly characteristic of VHL; specifically, bilateral occurrences are considered pathognomonic for the disease. Although these lesions are non-cancerous and often asymptomatic, they can occasionally cause infertility if they obstruct reproductive ducts on both sides. Previous reviews reported that approximately 25-60% of patients with PC had VHL [1, 2]. PCs most commonly arise in the epididymis of male patients with VHL. In contrast, its occurrence in females is distinctly rare. PCs in females may pose diagnostic challenges due to their morphological overlap with metastatic renal cell tumors. Here, we report a rare case of multiple PCs in a female patient with VHL along with a review of the relevant literature notably from the aspect of the immunohistochemical findings relevant to diagnosis.

https://doi.org/10.62347/MJHW3278

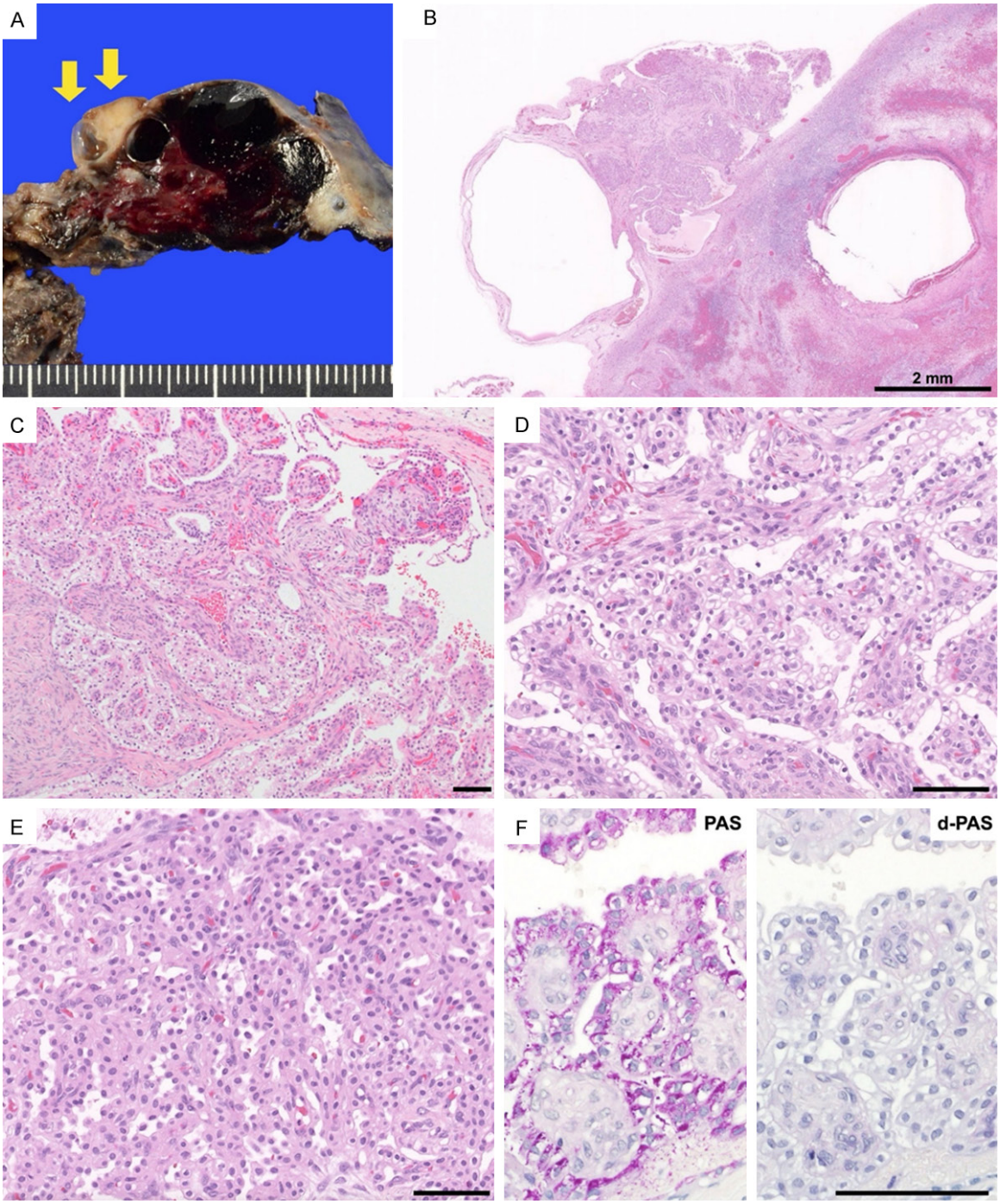

Figure 1. Pathological findings of the right ovary. A: The right ovary with hemorrhage was fragmented. There is a white solid nodule (7 × 5 × 4 mm in size; arrows) with cysts on the ovarian surface. B: The loupe image of the nodule. C: Variably-papillary projection into cysts. Tubular structures are also observed. D: The tumor papillae are lined by a monolayer of cuboid or columnar cells with clear cytoplasm. Neither nuclear atypia nor mitotic figure is observed. E: Tumor cells with eosinophilic cytoplasm are also partly seen. F: The tumor cells have glycogen-rich cytoplasm. Left; Periodic acid Stiff (PAS) staining, Right; PAS with diastase predigestion. Scale bar, 100 μm unless otherwise specified.

Case presentation

The patient is a 34-year-old woman. She was admitted to Akita University Hospital because of right lower abdominal pain ever since her waking up on that morning. Written comprehensive informed consent, including publication of a case report, was obtained from the patient.

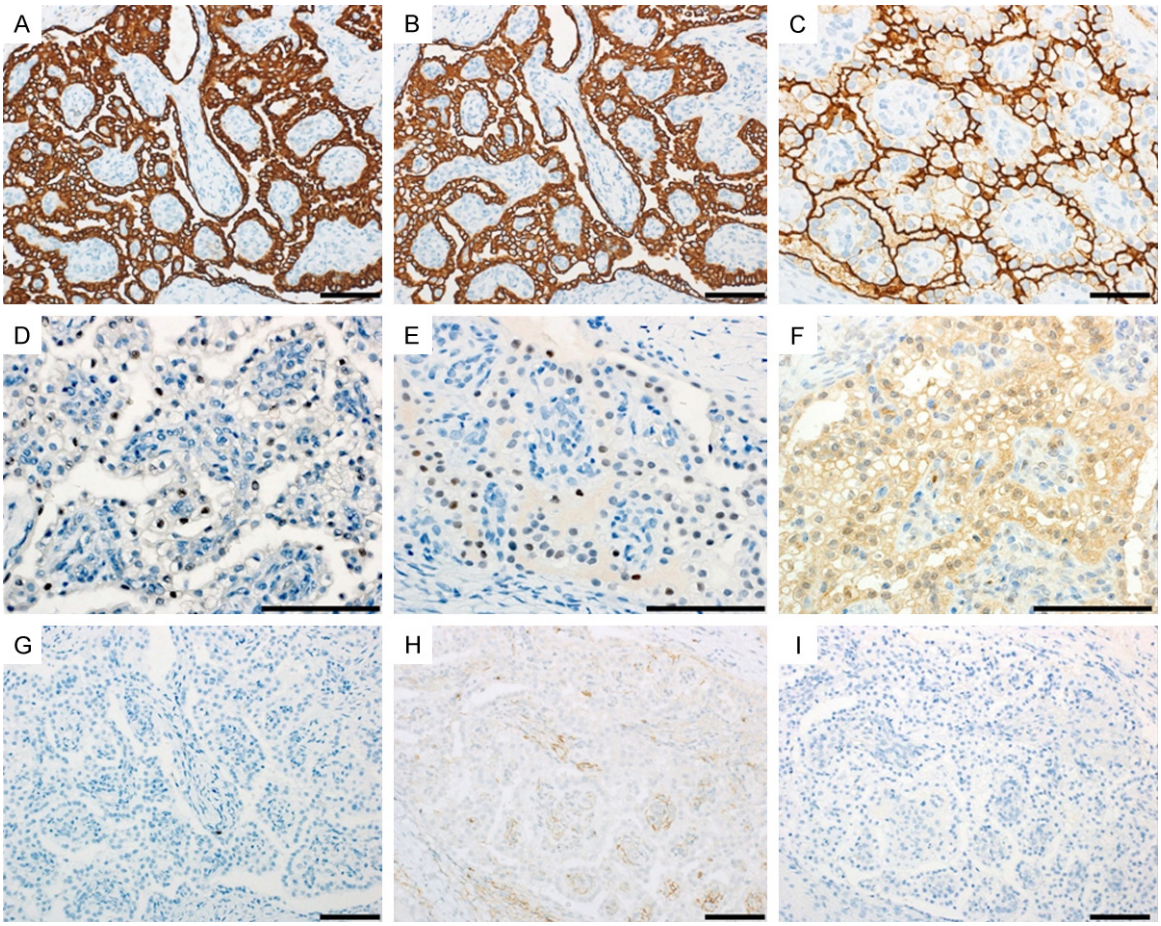

Figure 2. Immunohistochemical findings of the tumor. The tumor cells are diffusely positive for pan-keratin (AE1/AE3) (A), CK7 (B), and CA125 (C). (C) CA125 is positive at apical membranes. PAX8 (D) and GATA3 (E) are positive in nuclei weakly and partially. (F) Both cell membrane and cytoplasm of the tumor cells are diffusely positive for GST-μ. CK20 (G), CD10 (H), and RCC-ma (I) are negative. Scale bar, 100 μm.

All procedures used in this report were approved by Ethics Committee of Akita University Hospital (Approval Number: 2532). Ultrasonography and computed tomography revealed swelling of the right ovary (90 × 50 mm in size) and a small amount of ascites. A blood test indicated no abnormal values in different tumor markers. Findings of reduced blood flow into the right ovary led to the diagnosis of right ovarian torsion and thus right salpingo-oophorectomy was performed on the same day.

Her past medical history included VHL complex composed of multiple hemangioblastomas of the central nervous system and retinae, a pancreatic neuroendocrine tumor (NET), multiple foci of clear cell renal cell carcinomas (CCRCCs) of the bilateral kidneys, and multiple renal cysts. Hemangioblastomas were resected several times during those 15 years. Total pancreatectomy for NET had previously been performed. In addition, the PC of the left ovary was resected 7 years before. For multiple CCRCCs, cryogenic surgery had previously been implemented.

Macroscopically, the right ovary was fragmented and looked hemorrhagic. The cut section showed a solid white nodule (7 × 5 × 4 mm in size) with multilocular cysts on the ovarian surface (**Figure 1A**).

Microscopically, the nodule was adhered to the surface of the right ovary without invasive growth (**Figure 1B**). Epithelial cells displayed a proliferation pattern arranged in papillary or tubular structures (**Figure 1C**). The tumor cells had small oval nuclei and pale to eosinophilic cytoplasm (**Figure 1D** and **1E**). No apparent nuclear atypia, necrosis, or mitosis was seen.

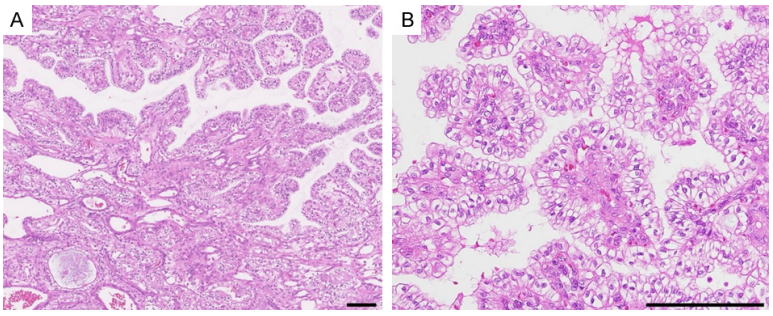

Figure 3. Findings of the left ovarian tumors. A, B: Clear cells without nuclear atypia are proliferating in papillary and glandular structures, similar to the tumor of the right ovary. Scale bar, 100 μm.

Periodic acid-Shiff (PAS) and PAS-diastase stains demonstrated glycogen deposition into the clear cy-toplasm of the tumor cells (**Figure 1F**).

Immunohistochemically, the tumor cells were diffusely positive for pan-keratin (AE1/AE3) (**Figure 2A**), keratin 7 (CK7) (**Figure 2B**), CA125 (**Figure 2C**), and vimentin (data not shown). Both PAX8 (**Figure 2D**) and GATA3 (**Figure 2E**) were positive although their positivity was, in general, weak and focal. Furthermore, the cell membrane and cytoplasm of the tumor cells were positive for glutathione S transferase mu (GST-μ) (**Figure 2F**). On the other hand, the tumor cells were negative for keratin 20 (CK20) (**Figure 2G**), CD10 (**Figure 2H**), and the renal cell carcinoma marker (RCC-ma) (**Figure 2I**). Based on histological findings and medical history, we diagnosed this tumor as PC. In the ovarian parenchyma, severe hemorrhage and multiple cysts including corpus luteum and follicle cysts were observed consistently with the ovarian torsion. **Figure 3** presents micrographs of the left ovarian tumor resected seven years earlier. Proliferating cells were histologically similar to those of the above-presented right ovarian tumor.

Discussion

PC is a benign epithelial tumor associated with VHL. In male VHL patients, it usually develops in the epididymis or epididymal duct. The incidence is relatively high as reported in 25-60% of male VHL patients. In contrast, PC is infrequent in females with its frequency and age of onset unknown in VHL patients [1, 2]. Bilateral PCs are twice as likely to occur with VHL as unilateral PCs [3-6]. Cases of multiple PCs in female VHL patients, however, have rarely been discussed in the literature. Therefore, we have felt that the present case is worth reporting. The bilateral occurrence is a finding that strongly suggests an association with VHL. The origin of PC is thought to be a Wolffian (mesonephric) remnant in females regardless of presence or absence of VHL [7, 8]. Wolffian remnant can be detected in various areas around the female genital tract. Actually, some reports on female VHL patients described that the locations of PC included the mesosalpinx, ovary, fallopian tube, and broad ligament [3, 7-14], all of which coincide with the regions where Wolffian remnants are found out. Also in our case, the tumors were located in the mesosalpinx and the vicinity of the ovarian hilum, so these findings indicate that the origin is a Wolffian remnant such as epoophoron and paroophoron.

Since microscopic findings of PC on hematoxylin and eosin stain are distinctly characteristic, its diagnosis is considered not difficult. Although our case is also typical in both morphological and immunohistochemical features, it is necessary to exclude the possibility of metastatic tumors in advance of diagnosing a tumor as VHL-related PC. Notably, it should be noted that about 30% of VHL patients develop renal cell carcinoma, the histotype of which is almost always CCRCC [1-3], manifesting partly-overlapping histological features with PC. Metastatic CCRCC should thus be considered to be a differential diagnosis in VHL patients. There are several reports which focus on these points. The authors described that CK7, CD10, and RCC-ma were useful to distinguish between PC and CCRCC [6, 8, 12]. CD10 and RCC-ma are positive, and CK7 is negative in metastatic CCRCCs. In our case, tumor cells are positive for CK7 but negative for CD10 and RCC-ma. However, there are some notes of caution in the diagnosis. Firstly, Aydin et al. [11] uncovered that CD10 tended to be positive in the PCs in female VHL patients but negative in the male PCs developed in the epididymis [6]. We should judge immunohistochemical findings carefully and should not make decisions based on a single marker positivity alone. Secondly, there was

Table 1. Immunohistochemical profiles of our case and differential diagnosis

Antigen	Pan-CK	CK7	CK20	Vimentin	RCC-ma	CD10	CA-IX	PAX8	GATA3	GST-μ	References
Our case	+	+	-	+	-	-	+*	+	+	+	N/A
PC	+	+	-	+	-	±	+*	+	ND	ND	[2, 6, 7, 12]
CCRCC	+	-	-	+	+	+	+	+	-	ND	[3, 4]
CCPRCC	+	-	-	+	ND	-	+*	+	+	ND	[3, 4]
Wolffian duct	+	+	-	+	ND	+	ND	+	+	+	[18-20]

PC, papillary cystadenoma; CCRCC, clear cell renal cell carcinoma; CCPRCC, clear cell papillary renal cell carcinoma; ND, not done; N/A, not applicable; Pan-CK was detected by the antibody AE1/AE3. *, cup-like pattern; +, positive in ≥50% of cases; -, negative in >50% of cases; ±, variable depending on affected sites, i.e., positive in the ovary but negative in the epididymis.

only one case where PC and metastatic CCRCC coexisted [15]. When a patient has a medical history of CCRCC, it is important to keep in mind CCRCC and to diagnose it studiously. Finally, it has been described that VHL patients sometimes develop clear cell papillary renal cell carcinoma (CCPRCC) [16, 17]. PC and CCPRCC display similar immunohistochemical findings, i.e., positive for CK7 and CA-IX and negative for RCC-ma [4, 17]. Therefore, it is necessary to make a diagnosis based on a comparison with the histological type of renal cancer in the past. Although clear cell carcinoma of the female genital tract may also be considered to be a differential diagnosis in female VHL patients, it is easy to rule it out based on cellular atypia. A summary of immunohistochemical findings from several reports is presented in **Table 1**. It has been reported that the female Wolffian duct-derived lesions including mesonephric duct remnant, hyperplasia, and mesonephric duct carcinoma are positive for PAX8, GATA3, and GST-μ [18-20]. GST-μ is also expressed in the testis, epididymis, seminal vesicles, and subsets of renal tubules. In our case, the tumor cells of PC expressed GST-μ (clone ab268069, Abcam) in addition to PAX8 and GATA3. Although the majority of published literature on PC describes PAX8 staining, no literature has ever referred to immunohistochemical findings of GATA3 and GST-μ. Furthermore, CCPRCC is usually positive for GATA3, but CCRCC is negative. In the future, GATA3 and GST-μ may also become useful markers for PCs derived from mesonephric ducts and for exclusion of metastatic CCRCC.

Conclusion

In conclusion, papillary cystadenoma in female patients with VHL is rare and can be diagnostically challenging. Immunohistochemistry plays a pivotal role in its accurate diagnosis. Our case provides additional insight into this uncommon entity.

Acknowledgements

The authors are grateful to Ms. Saori Suda and Ms. Reiko Ito for their technical assistance and Ms. Eriko Kumagai for her secretarial work.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yasufumi Omori, Department of Molecular and Tumour Pathology, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan. Tel: +81-18-884-6061; Fax: +81-18-836-2601; E-mail: yasu@med.akita-u.ac.jp

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