Advances in Obstetrics and Gynecology Research, 2026, Volume 4, Issue 2
http://ojs.bbwpublisher.com/index.php/AOGR
Online ISSN: 2981-8060
Print ISSN: 3083-4872

Case Analysis of Cervical Cancer Complicated with Von Hippel-Lindau Syndrome

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Abstract: *Objective*: To explore the clinical characteristics, diagnostic approach, and multidisciplinary management strategies of cervical cancer complicated with Von Hippel-Lindau syndrome (VHL), and to enhance clinical awareness of rare and complex cases. *Methods*: A retrospective analysis was conducted on the clinical data of a patient with cervical cancer complicated by VHL syndrome. The patient's medical history, family genetic background, laboratory tests, imaging findings, pathological results, diagnostic process, and multidisciplinary treatment were organized and analyzed in conjunction with relevant literature. *Results*: The patient was a 77-year-old female presenting with vaginal bleeding and lower abdominal distension. Cervical biopsy pathology indicated cervical squamous cell carcinoma, staged as IIIC1r. Further examination revealed abnormal changes in multiple systems, including the liver, pancreas, kidneys, and adrenal glands, along with a clear family genetic background of VHL. After comprehensive evaluation through imaging, pathology, and multidisciplinary consultation, the patient was ultimately diagnosed with cervical cancer complicated by VHL syndrome. This case was characterized by advanced age at onset, pronounced family clustering, multi-organ involvement, and complex diagnosis and treatment. *Conclusion*: Cervical cancer complicated by VHL syndrome is relatively rare in clinical practice. For patients with a special family history and multi-system involvement, it is essential to enhance awareness of hereditary tumor syndromes, strengthen multidisciplinary collaboration, and conduct individualized assessments to improve the diagnostic proficiency and clinical management capabilities for complex cases.

Keywords: Cervical cancer; Von Hippel-Lindau syndrome; VHL syndrome; Multidisciplinary treatment; Case analysis

Online publication: May 31, 2026

1. Introduction

Von Hippel-Lindau (VHL) syndrome is a rare autosomal dominant disorder characterized by multiple tumors and cysts in various organ systems. Cervical cancer is not a classic component of VHL syndrome, and its coexistence is extremely rare. Here, we present a case of a 77-year-old female with locally advanced cervical squamous cell carcinoma concurrently diagnosed with VHL syndrome, highlighting the diagnostic and

management challenges of such rare complex cases.

2. Medical condition presentation

The patient, a 77-year-old female from Hebei Province, was admitted to the hospital due to "intermittent vaginal bleeding for over three months accompanied by lower abdominal distension and pain." Since January 2026, the patient has experienced intermittent, slight vaginal bleeding without apparent cause, which is bright red, intermittent, and without significant blood clots, accompanied by a sensation of lower abdominal distension and mild pain in the lower back, without notable symptoms such as frequent urination, urgency, or constipation. She sought medical attention at the Affiliated Hospital of Hebei University, where a gynecological examination revealed a cervical mass, prompting further investigations. A gynecological ultrasound indicated reduced local echo in the cervix, measuring approximately 3.1 cm × 1.2 cm, with unclear borders. TCT showed atypical squamous cells, and HPV16 was positive. A cervical biopsy pathology report indicated a malignant tumor, consistent with squamous cell carcinoma, based on immunohistochemical results. Immunohistochemistry results showed: P40 (+), P63 (+), P16 (+), Ki-67 (70%+), CK7 (+), EGFR (+). Relevant case data were sourced from uploaded medical records. The patient has a history of hypertension for over 30 years, treated with long-term oral amlodipine besylate and valsartan; diabetes for over 20 years, controlled with long-term Novolin 30R. She has smoked for over 50 years, approximately 7-8 cigarettes per day, with no history of alcohol consumption, trauma, blood transfusion, or major surgery. The family history is notably distinctive. The patient's son carries the VHL gene; her brother underwent surgical treatment for central nervous system and renal tumors; both sisters died from multiple tumors; her nephew was diagnosed with VHL syndrome, indicating a familial clustering of the disease.

Upon admission, physical examination revealed an obese body type with a BMI of 26.8, clear consciousness, and no palpable enlargement of superficial lymph nodes. Gynecological examination showed the disappearance of the original cervical shape, with an irregular, hard mass on the surface measuring approximately 5 cm × 4 cm, significantly invading the left parametrium, disappearance of the vaginal fornix, and thickening of the left parametrium reaching the pelvic wall, which was fixed. A tripartite examination indicated that the sacral ligaments were not thickened, the rectal mucosa was smooth, the left parametrium was significantly thickened, reaching the pelvic wall and fixed, and the right side was slightly thickened.

Pelvic MRI revealed a localized mass-like abnormal signal in the cervix, measuring approximately 2.8 cm × 2.7 cm × 3.0 cm, with the lesion invading the upper one-third of the vagina and the left parametrium, extending to the pelvic wall, and enlarged lymph nodes beside the left iliac vessels. Thoracoabdominal pelvic enhanced CT showed scattered nodules in both lungs, multiple liver cysts, multiple pancreatic cysts, multiple left renal cysts, multiple right renal space-occupying lesions, and bilateral adrenal nodules, suggesting the possibility of VHL syndrome.

Laboratory tests showed: white blood cells at 11.71 × 10^9/L; significantly elevated urinary white and red blood cells; D-dimer at 0.70 μg/mL; glycated hemoglobin at 10.4%; significantly elevated squamous cell carcinoma antigen at 8.850 ng/mL.

3. Diagnostic basis

The patient, an elderly female, presented primarily with vaginal bleeding and lower abdominal distension.

Gynecological examination revealed a space-occupying lesion in the cervix, and cervical biopsy pathology confirmed squamous cell carcinoma. Pelvic MRI showed parametrial and pelvic wall invasion, along with pelvic lymph node metastasis, meeting the diagnostic criteria for stage IIIC1r cervical cancer. The patient has a typical VHL family genetic background, with multiple first- and second-degree relatives having a history of VHL-related tumors. Imaging studies revealed multiple renal space-occupying lesions and cysts, multiple pancreatic cysts, liver cysts, and bilateral adrenal lesions, consistent with the multi-system involvement characteristic of VHL syndrome. Although cranial MRI did not reveal hemangioblastomas, the diagnosis of VHL syndrome does not rely on a single organ manifestation but requires a comprehensive analysis based on genetic background and multi-organ imaging features [1]. MDT discussion concluded that the diagnosis of VHL syndrome was established.

4. Diagnostic results

(1) Cervical squamous cell carcinoma, stage IIIC1r;
(2) Von Hippel-Lindau syndrome (VHL syndrome);
(3) Right renal space-occupying lesion (suspected clear cell renal carcinoma);
(4) Multiple pancreatic cysts;
(5) Multiple liver cysts;
(6) Bilateral renal cysts;
(7) Type 2 diabetes mellitus;
(8) Hypertension.

5. Analysis report

Von Hippel-Lindau syndrome (VHL) is a rare autosomal dominant hereditary tumor syndrome caused by mutations in the VHL tumor suppressor gene located on the short arm of chromosome 3 (3p25-26). The VHL gene encodes a protein involved in the degradation regulation of hypoxia-inducible factor (HIF). When the VHL gene undergoes loss-of-function mutations, HIF cannot be normally degraded, continuously activating downstream pro-angiogenic factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF), further promoting abnormal angiogenesis, cell proliferation, and tumorigenesis. Given its involvement in metabolic regulation in multiple tissues and organs, VHL syndrome is characterized by multi-organ, multifocal, and lifelong progression [2].

The clinical manifestations of VHL syndrome are complex and can involve multiple organ systems, including the central nervous system, kidneys, adrenal glands, pancreas, reproductive system, retina, and inner ear. Classic manifestations include central nervous system hemangioblastomas, clear cell renal carcinoma, renal cysts, pancreatic cysts, pheochromocytomas, endolymphatic sac tumors, and epididymal cystadenomas. Literature reports an incidence of approximately 1/36,000, with over 95% of patients developing initial symptoms before age 34 and nearly 100% penetrance after age 70. The average lifespan is approximately 59.4 years for males and 48.4 years for females, with central nervous system hemangioblastomas and renal cell carcinoma being the primary causes of death. Relevant case data also suggest that VHL syndrome is a hereditary disease characterized by multi-system, multi-organ tumorigenesis.

This patient, at 77 years old, was first systematically identified and diagnosed with VHL syndrome,

significantly later than the commonly reported age of onset in the literature, which is a rare occurrence. Further analysis reveals a prominent family genetic background. Both of the patient's sons carry the VHL gene; her brother underwent surgical treatment for central nervous system and renal tumors; both sisters died from multiple tumors throughout the body; her nephew was diagnosed with VHL syndrome after surgical treatment for a central nervous system tumor at a superior hospital, indicating a clear familial clustering of the disease. These characteristics are consistent with an autosomal dominant inheritance pattern. The risk of VHL syndrome in first-degree relatives can reach 50%, making family history crucial for disease diagnosis.

Imaging studies showed scattered tiny nodules in both lungs, multiple liver cysts, multiple pancreatic cysts, multiple left renal cysts, a space-occupying lesion in the right kidney, and bilateral adrenal nodular thickening on thoracoabdominal pelvic enhanced CT. The right renal lesion is suspected to be clear cell renal carcinoma, while the pancreas and liver primarily exhibit cystic lesions, consistent with the common distribution of affected organs in VHL syndrome. Although cranial MRI enhancement did not reveal central nervous system hemangioblastomas, and fundus examination did not find retinal hemangiomas, VHL syndrome exhibits significant clinical heterogeneity, and not all patients present with a complete disease spectrum. Some patients may initially present with abnormalities in only one system, necessitating a comprehensive judgment based on family history, imaging, and organ involvement.

On the other hand, this patient also has cervical squamous cell carcinoma. Cervical cancer is a common malignant tumor in the female reproductive system, closely related to persistent high-risk HPV infection, with HPV16 being the primary high-risk subtype. This patient tested positive for HPV16, and TCT indicated atypical squamous cells. Biopsy pathology, combined with immunohistochemical results, confirmed the diagnosis of squamous cell carcinoma. Immunohistochemistry showed positive P16 expression and a Ki-67 proliferation index of 70%, indicating active tumor cell proliferation, consistent with the molecular biological characteristics of HPV-related cervical cancer.

Pelvic MRI further indicated a cervical lesion measuring approximately 2.8 cm × 2.7 cm × 3.0 cm, with the lesion invading the upper one-third of the vagina, left parametrial tissue, and pelvic wall, accompanied by enlarged lymph nodes beside the left iliac vessels. Gynecological examination revealed the disappearance of the original cervical shape, with an irregular, hard mass significantly invading the left side, disappearance of the vaginal fornix, and thickened parametrial tissue reaching and fixing to the pelvic wall. Combined with imaging and clinical manifestations, this is consistent with the presentation of locally advanced cervical cancer, stage IIIC1r.

The uniqueness of this case is mainly reflected in the following aspects. First, the co-occurrence of VHL syndrome and cervical cancer is extremely rare, with few related reports domestically and internationally, and cervical cancer is not part of the classic tumor spectrum of VHL, so there is a lack of clear research evidence on whether there is a common molecular mechanism between the two. Second, the patient simultaneously has renal space-occupying lesions, pancreatic cysts, liver cysts, and adrenal lesions, requiring differentiation between metastatic lesions, secondary tumors, and VHL-related lesions. Third, the patient is elderly and has comorbidities such as diabetes, hypertension, and a long smoking history, increasing treatment risks and diagnostic and therapeutic challenges. Fourth, this case involves issues in gynecological oncology, genetics, imaging, pathology, and multidisciplinary comprehensive management, making it a typical complex case.

Therefore, this case is not a simple case of cervical malignancy but a complex and special case influenced by genetic background, multi-system involvement, and advanced age with comorbidities. For such

patients, clinical management should not only focus on controlling the primary lesion but also emphasize screening for systemic lesions, genetic counseling, and family management. Multidisciplinary collaboration is essential to achieve precise and individualized diagnosis and treatment, providing a reliable basis for long-term disease management.

6. Treatment plan

Given the patient's complex condition, the focus of treatment is on controlling local cervical lesions while simultaneously assessing the risk of VHL-related lesions. For general treatment, nutritional support and management of underlying diseases are provided, with enhanced monitoring of blood glucose and blood pressure to control risk factors. For VHL syndrome, a comprehensive systemic screening is conducted, including brain MRI, fundus examination, urinary system imaging, and multi-organ evaluation to determine the extent of involvement. Ophthalmology consultation and OCT reveal diabetic retinopathy and cataracts in both eyes; brain MRI does not reveal any mass in the central nervous system. After the patient's admission, an MDT multidisciplinary consultation is held, involving pathology, urology, radiology, and hepatobiliary surgery departments. Pathology suggests a full genetic blood test due to the patient's family history of VHL; urology considers the possibility of clear cell renal carcinoma in the right kidney; radiology recommends further PET-CT to assess the nature of the lesions; hepatobiliary surgery suggests no immediate intervention for pancreatic and liver cysts, recommending dynamic observation. After comprehensive analysis, it is determined that the current cervical cancer lesion is large, accompanied by significant vaginal bleeding and pelvic wall invasion, representing the primary issue at hand. Therefore, priority is given to addressing the cervical lesion.

7. Clinical measures

After integrating MDT opinions and fully communicating with the patient's family, and considering the patient's clear family history of VHL, the family requests prioritizing local treatment for cervical cancer and temporarily refuses PET-CT and hematological genetic testing. Subsequently, a precise pelvic radiotherapy plan is formulated, with the radiation target area covering the primary cervical lesion, bilateral obturator lymph nodes, and high-risk parametrial regions. GTVnd is defined as visible enlarged obturator lymph nodes. CTV includes the cervix, uterus, parametrium, and pelvic lymphatic drainage areas, with stratified dose designs based on different risk areas. The specific dose regimen is as follows: PTV is administered at 4500 cGy in 25 fractions, PTV1 at 5400 cGy in 25 fractions, PTV2 at 5200 cGy in 25 fractions, and PGTVnd at 6000 cGy in 25 fractions. Starting from the fourth weekend, CT-guided intravaginal three-dimensional brachytherapy is added, with a single dose of 600 cGy, planned for five sessions, ultimately achieving an EQD2 of $\geq$ 8500 cGy in the tumor area. During treatment, vital signs monitoring, blood glucose control, and nutritional support are conducted simultaneously, with continuous assessment of renal masses and changes in VHL-related lesions. Given the patient's advanced age and multi-organ disease background, close attention is paid to the risks of bone marrow suppression, urinary system injury, and complications during treatment. After local radiotherapy, once the overall condition improves, further consultation with urology for renal mass resection is planned, with close follow-up on masses and cysts in other organs throughout the body.

8. Summary and discussion

VHL syndrome is a rare hereditary tumor syndrome with complex clinical manifestations involving multi-system lesions [3]. This case involves an elderly patient with locally advanced cervical cancer, renal masses, and cystic lesions in the pancreas and liver, presenting a complex diagnostic process and challenging treatment decisions. Due to the rarity of concurrent cervical cancer and VHL syndrome, clinical experience is limited, necessitating enhanced recognition of family history and multi-system imaging abnormalities. For complex tumor patients, the MDT model should be emphasized, with joint decision-making across gynecology, pathology, genetics, imaging, and surgery to achieve individualized management. Particularly for patients with a genetic background, family screening and genetic counseling should be prioritized to improve early detection rates and provide a basis for subsequent precise treatment. This case can offer some reference for the diagnosis and treatment of clinically rare cases.

Disclosure statement

The authors declare no conflict of interest.

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