

## Case Report

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# HPV-Related Retroperitoneal Squamous Cell Carcinoma of Unknown Primary: A Case Report

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A 56-year-old female was referred to our hospital due to a mass measuring 5 cm in size in the left pelvic cavity, which was found incidentally during a health examination by ultrasonography. Exploratory laparotomy was performed and the mass was located at the left retroperitoneal parametrium without invasion of the uterus and ovary. The pathology report confirmed squamous cell carcinoma. Even after further studies, we did not find any other primary lesion. Human papillomavirus (HPV) DNA chip test (HPV 9G DNA Membrane Kit, Biometrixtechnology Inc.) showed that the surgical specimen was positive for HPV 18. She received adjuvant chemotherapy and would receive radiation therapy for the possibility of occult gynecologic cancer. Retroperitoneal squamous cell carcinoma of unknown primary is extremely rare and little is known about it. It is reported that HPV may be associated with the disease. Hence, the result of HPV test could have an impact on finding a suspicious primary lesion and treatment modality in this case.

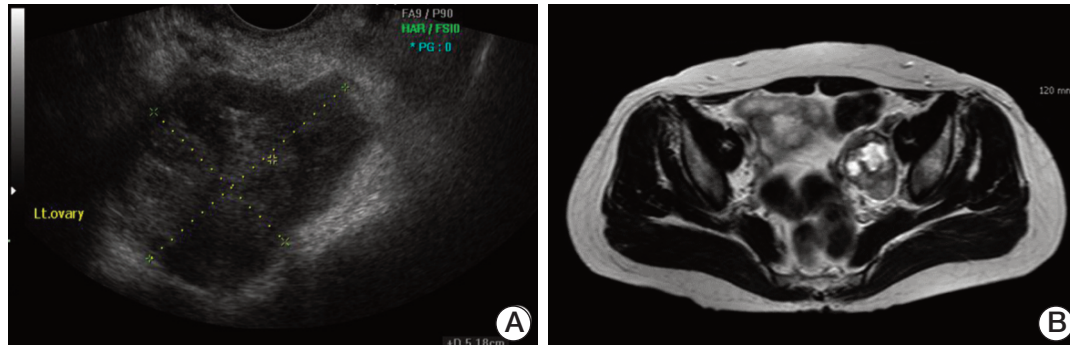
**Key words**

Retroperitoneal neoplasms, Squamous cell carcinoma, Human papillomavirus

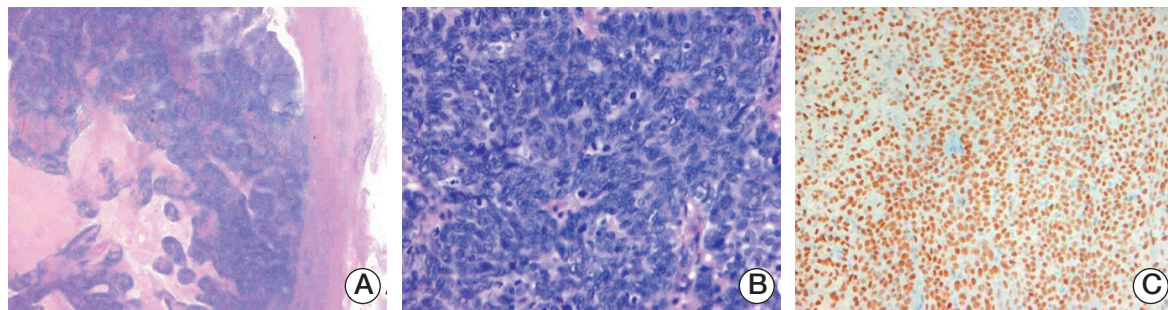
## Introduction

Retroperitoneal neoplasms, defined as solid or cystic tumors that arise within the retroperitoneal space, are rare and estimated to represent approximately 0.1%-0.2% of all malignant tumors, where most frequent entities include lymphoproliferative tumors, soft tissue tumors, and extragonadal germ cell tumors [1]. Retroperitoneal squamous cell

carcinoma (SCC) of unknown primary is extremely rare and little is known about its etiology, pathogenesis, and optimal therapy. Human papillomavirus (HPV), first discovered in the 1980s as a carcinogen, is usually associated with gynecologic malignancies. In this paper, we report on a case of HPV positive retroperitoneal squamous carcinoma of unknown primary. To the best of our knowledge, retroperitoneal squamous carcinoma of unknown primary has been reported once in Korea, and our case represents the first report of HPV



**Fig. 1.** (A) Transvaginal ultrasound demonstrated a left pelvic mass with complex echogenicity of 5.18 cm×3.68 cm. (B) T2 weighted pelvic magnetic resonance imaging showed a solid and cystic, heterogeneous enhanced mass measuring 5.5 cm in size in the left pelvic cavity.



**Fig. 2.** (A) Microscopic examination shows a well capsulated retroperitoneal mass (H&E staining, ×40). (B) Microscopic examination shows poorly differentiated squamous cell carcinoma (H&E staining, ×400). (C) Immunohistochemical staining of p63 shows strong nuclear positivity (×200).

positive retroperitoneal squamous carcinoma. Here, we report our case with a review of the literature.

## Case Report

A 56-year-old female was admitted to our hospital, due to abnormal abdominal ultrasound findings that were found incidentally during a regular check-up. The patient denied any symptoms and the presence of any specific medical or family history. She had reached her menopause 2 years ago and her regular Papanicolaou (Pap) smear tests had been normal so far.

The patient was hemodynamically stable on admission. On physical examination, her abdomen was soft and non-tender with no palpable mass. The laboratory findings were all within normal limits.

On gynecological examination, the cervix was normal and

Pap test was negative. Transvaginal ultrasound demonstrated a left pelvic mass with complex echogenicity of 5.18 cm×3.68 cm (Fig. 1A). Pelvic magnetic resonance imaging showed a solid and cystic, heterogeneous enhanced mass measuring 5.5 cm in size in the left pelvic cavity (Fig. 1B). Around the mass, there were suspicious metastatic lymph nodes in the left internal iliac region. Fluorodeoxyglucose positron emission tomography (FDG-PET) showed no other focus with increased glucose metabolism which excluded other origins of carcinoma or any metastatic location except the left pelvic mass. Endoscopy, colonoscopy, and cystoscopy were also normal. We also performed computed tomography (CT) of head, neck, and chest, which showed no abnormality. Tumor markers including carcinoembryonic antigen, cancer antigen (CA) 125, CA 19-9, alpha-fetoprotein,  $\beta$ -subunit of human chorionic gonadotropin, and SCC antigen were normal.

Subsequently, the patient underwent an exploratory laparotomy. The upper abdominal organs were grossly normal and the pelvic cavity was clean, with normal uterus

and bilateral adnexa. The mass was firm, well circumscribed, measuring 5.2×4.5×3.5 cm and located in the left retroperitoneal parametrium adjacent to the common iliac vessel, obturator nerve, and external iliac vessel. There was no invasion to the uterus and ovary. We performed complete resection of the tumor with left pelvic lymph node dissection. The tissue was poorly differentiated carcinoma. Immunohistochemistry of cytokeratin (CK) 7, CK 20, and thyroid transcription factor 1 were negative and CK 5/6 was positive. To investigate the focal lesion with squamous differentiation, additional immunohistochemistry staining of p63 was performed, which showed strong nuclear positivity. Considering the result, we concluded the final pathology as poorly differentiated SCC (Fig. 2A-C). The lymph nodes were negative for malignancy. In addition, HPV DNA chip test was performed using the HPV 9G DNA Membrane Kit (Biometrixtechnology Inc., Seoul, Korea) and the specimen was positive for HPV 18. Postoperative CT of the abdomen was performed and showed no remaining retroperitoneal mass. The patient underwent adjuvant chemotherapy with 5-fluorouracil (5-FU; 1,000 mg/m<sup>2</sup>) for four days and cisplatin (60 mg/m<sup>2</sup>) for one day every 4 weeks. After four-cycles of chemotherapy, we performed CT of neck, chest, and abdomen as follow-up evaluation, and it showed no evidence of disease. We planned additional radiotherapy.

## Discussion

To the best of our knowledge, the case presented here is the first description of a primary retroperitoneal SCC with the positivity of HPV 18 in South Korea. Currently, FDG-PET is one of the preferred imaging modalities used in detection of carcinoma of unknown primary origin. In this patient, FDG-PET did not show any occult carcinoma. Other studies including endoscopy, colonoscopy, cystoscopy, and chest CT were normal and all tumor markers were negative. It has previously been reported that SCC from the head and neck region rarely metastasizes as a solitary pelvic mass [2]. We performed CT of the head and neck, and laryngoscopy, but could not find any lesions. Because all of the imaging test results were negative, and a retroperitoneal mass was located adjacent to the urogenital organs, we performed additional molecular examination by HPV DNA chip test, which revealed HPV 18 positive.

It is believed that HPV contributes to development of a carcinoma through a combination of loss of cell cycle differentiation and genomic instability. It is established that HPV infection is associated with anal, cervical, vulvar, penile, and vaginal cancer. In addition, HPV infection is implicated in

head and neck SCC, particularly oropharyngeal cancer [3]. HPV test has been used to differentiate primary gynecologic malignancies when the etiology is unclear. In a study by Staebler, HPV testing was used to differentiate endometrial from endocervical cancer [4]. HPV was positive in 16 out of 24 endocervical cases (66.7%) compared to 0 out of 24 endometrial cases. Our case appears to be the first case describing retroperitoneal pelvic masses with unknown primary that are HPV 18-positive, despite normal cervical examination and cytology.

Direct exposure and infection by HPV are thought to be the main routes. In a malignancy that does not arise from surface or mucosal tissues, the route of transmission is less clear. However, in many reports, transmission of HPV has been reported to occur through many routes, including sexual transmission, oral cavity, lymphatic or hematogenous spread [5-7]. In this case, we could not find the exact route of HPV-infected tumor cells because of unknown primary origin. However, we could hypothesize that multiple routes could be possible and that HPV infection played an important role in carcinogenesis.

The importance of complete surgical resection has been emphasized in the literature as it is believed to be directly related to patient survival [1,8,9]. In order to exclude metastasis from primary gynecological malignant lesions, total hysterectomy with bilateral salpingo-oophorectomy is often performed. In addition, pelvic lymphadenectomy, paraaortic lymphadenectomy, and omentectomy could be considered [10-12]. In our patient, no lesion was observed on PET-CT with negative tumor markers and complete resection was considered possible and was therefore performed.

HPV test affects the modality of treatment and increases the likelihood of performing radiotherapy or chemoradiotherapy, which improves clinical outcome. The role of radiation or chemoradiation in the treatment of cervical cancer is well known. We found that HPV-positive head and neck SCC, when treated with chemoradiation has better clinical outcomes than HPV-negative cancers [13,14]. Due to the rarity of retroperitoneal SCC, there is no well-established chemotherapy or radiotherapy regimen. In some case series and reports, retroperitoneal SCC treated with chemoradiation had better prognosis compared with patients who were not treated with additional radiation [5,8]. In our case, the patient underwent adjuvant chemotherapy with the use of 5-FU/cisplatin for four cycles to prevent systemic relapse [13,14]. We also plan to perform additional radiotherapy after chemotherapy because of high local recurrence rate and poor prognosis of primary retroperitoneal SCC.

We have presented a case of retroperitoneal SCC of unknown primary that was HPV-positive. Surgical resection was performed followed by adjuvant chemotherapy with 5-FU/cisplatin. Complete surgical resection in our case is

expected to produce a good result, although further observation for local recurrence and metastasis is needed. HPV may be associated with pelvic masses of unknown primary, even in patients with normal cervical examination results. Hence, the result of HPV test could have an impact on finding suspicious primary lesion and treatment modality in our case.

## Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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