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Clinical Analysis of Cervical HSIL with Poorly Differentiated Squamous Cell Carcinoma Metastatic to the Ovary

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Abstract: *History summary*: A 64-year-old female patient presented with a three-month history of right lower abdominal pain. Ultrasound examination revealed a mass measuring approximately 5 cm × 4 cm × 4 cm in the right adnexal region, which was movable with slight tenderness. The ultrasound suggested a cystic-like mass in the right adnexal region, and "pelvic mass" was considered. *Family history*: The patient's mother died of "ovarian cancer" (specific pathological type unknown), and her sister was diagnosed with "breast cancer" (positive for BRCA1 gene testing). *Symptoms and signs*: The patient experienced dull pain in the right lower abdomen accompanied by a slight sensation of fullness in the lower abdomen. On bimanual examination, a mass measuring approximately 5 cm × 4 cm × 4 cm was palpable in the right adnexal region, which was movable with slight tenderness. *Diagnostic methods*: Ultrasound suggested a cystic-like mass in the right adnexal region. CT examination revealed a low-density mass in the right adnexal region with slight thickening of the adjacent intestinal wall, suggesting an ovarian origin. *Treatment*: Laparoscopic total hysterectomy + bilateral adnexectomy + pelvic and para-aortic lymph node dissection + omentectomy + peritoneal multi-point biopsy. *Final diagnosis*: Pathological consultation at a superior hospital confirmed (cervical) HSIL (CINII grade) and poorly differentiated squamous cell carcinoma of the ovary (metastatic origin). The patient was considered to have poorly differentiated squamous cell carcinoma associated with HPV infection originating from the cervix and metastasizing to the right ovary.

Keywords: HSIL; HPV infection-related; Squamous cell carcinoma metastatic to the ovary

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1. Introduction

Cervical cancer is one of the malignant tumors in women, with primary routes of metastasis including direct spread, lymphatic metastasis, and hematogenous metastasis. Direct spread is the most common early mode of metastasis, where cancer cells first spread to adjacent tissues, invading the bladder anteriorly, the rectum

posteriorly, the parametrial tissues, cardinal ligaments, uterosacral ligaments, and pelvic wall laterally, the vaginal wall inferiorly, and the uterine body superiorly in rare cases. When cancer cells invade the lymphatic vessels, they typically metastasize sequentially according to the direction of lymphatic drainage. Hematogenous metastasis generally occurs in the late stages, with cancer cells spreading to distant organs through the bloodstream, commonly to the lungs. Metastasis to the ovaries is extremely rare. Poorly differentiated squamous cell carcinoma metastatic to the ovary from cervical HSIL is even more difficult to believe.

2. Clinical data

2.1. General information

The patient, a 64-year-old female, was admitted to the hospital primarily due to lower right abdominal pain for three months. Three months ago, the patient experienced dull pain in the lower right abdomen without obvious precipitating factors, accompanied by a slight sensation of fullness and heaviness in the lower abdomen. There was no vaginal bleeding or discharge, nor any other symptoms such as nausea or vomiting. She sought medical attention on October 28, 2025.

Past Medical History: No history of hypertension, diabetes, or coronary heart disease. Family History: The patient's mother died of "ovarian cancer" (specific pathological type unknown), and her elder sister was diagnosed with "breast cancer" (positive for BRCA1 gene mutation).

2.2. Examination

2.2.1. Abdominal examination

The abdomen was flat and soft, with mild tenderness in the lower right abdomen. No masses were palpable. Gynecological Examination: Married vulva, patent vagina, atrophic cervix with a smooth surface, normally positioned uterus of normal size, medium consistency, good mobility, and no tenderness. A mass measuring approximately 5 cm × 4 cm × 4 cm was palpable in the right adnexal region, with good mobility and mild tenderness. No obvious abnormalities were detected in the left adnexal region.

2.2.2. Gynecological ultrasound

The uterus was in an anterior position, with a size of 3.8 cm × 2.8 cm. The anterior and posterior borders of the uterine body were clear, and the echo of the uterine muscle wall was uneven. Multiple hypoechoic nodules were visible in the intermuscular layer of the anterior wall of the fundus. The endometrium was centrally located, with a cervical size of 2.2 cm × 1.9 cm. The left ovary measured 1.3 cm × 0.5 cm, and a hypoechoic mass measuring 5.0 cm × 3.6 cm was visible in the right adnexal region, with a regular shape but unclear borders. It appeared to contain a poorly sonolucent cystic area with interspersed strong echo spots and no obvious blood flow signals. The right ovary was not clearly visualized. Indications: Multiple solid masses in the uterine wall (considering myomas) and a cystic-like mass in the right adnexal region.

2.2.3. CT examination

Suggested a low-density mass shadow in the right adnexal region, with slight thickening of the adjacent intestinal wall.

Tumor Markers (October 26, 2025): CA125: 6.46 U/mL, CA72-4: 0.9 U/mL, CA199: 26.2 U/mL, CEA: 1.62 ng/mL, AFP: 3.48 ng/mL, HE4: 51 U/mL, SCC: 0.5 ng/mL. HPV DNA-56 (high-risk type) positive (+),

HPV DNA-58 (high-risk type) positive (+), HPV DNA-6 (low-risk type) positive (+). TCT results showed a small number of DNA ploidy abnormal cells. TBS diagnosis: Atypical epithelial cells. Colposcopy showed non-staining areas with the iodine test, and cervical tissue biopsy was sent for pathology. Results: (Cervical) HSIL (CIN Grade 2). Immunohistochemistry results: P16 (+), Ki-67 (2/3+ in the squamous epithelium). (Family refused conization).

3. Diagnosis

Preliminary Diagnosis: (1) Pelvic mass; (2) Multiple uterine leiomyomas.

4. Treatment

(1) Surgical Treatment

Laparoscopic exploration was performed on October 31, 2025. Intraoperatively, the uterus was enlarged to the size of a 50+ day pregnancy, with multiple myoma nodules in the muscle wall. The right ovary was solidly enlarged to 6 cm × 5 cm × 4 cm, with a hard consistency and dense adhesion to part of the rectum and the right pelvic wall. The right ureter passed through it, and the right fallopian tube and left adnexa appeared normal. No enlarged lymph nodes were detected beside the pelvic aorta. No lesions were found on the surface of the omentum. The right adnexa was resected and sent for frozen pathology: severe hemorrhage and necrosis of the tumor-like tissue, with degenerated atypical cells visible, not excluding poorly differentiated carcinoma. Due to the hard consistency of the right ovarian mass, dense adhesion to surrounding tissues, and the passage of the ureter through it, making separation difficult, a "laparoscopic total hysterectomy + bilateral adnexectomy + pelvic and para-aortic lymph node dissection + omentectomy + multipoint peritoneal biopsy + cystoscopic right ureteral stent (D-J tube) placement" was performed.

(2) Postoperative pathology results

Left adnexa (-), multiple uterine leiomyomas, senile endometrium. Chronic cervicitis and endometritis, negative for the uterine serosal surface, omental tissue (-). Left colonic sulcus peritoneum (-), right colonic sulcus peritoneum (-), intestinal surface mass: a small number of degenerated atypical cells were visible in the fibrofatty tissue. Ureteral surface mass tissue: infiltration of poorly differentiated carcinoma was visible. Right adnexal mass (frozen residue and paraffin): a small number of degenerated atypical cells were visible in the degenerated necrotic tissue, not excluding poorly differentiated carcinoma. Immunohistochemistry results: AE1/AE3 (+), Vimentin (+), ER (-), PR (-), P16 (-), CA125 (+/-), WT1 (-), Ki67 (80% positive cells), CK7 (+), CK20 (-), Pax-8 (-), HNF1β (-), P40 (-), GATA3 (-), SALL4 (-), CDX2 (-). Based on immunohistochemical expression and histological morphology, infiltration of poorly differentiated carcinoma was visible in the fibrous and muscular tissues.

According to the postoperative pathology and immunohistochemistry results, the discharge diagnosis was revised to: (1) Ovarian poorly differentiated carcinoma Stage IIB; (2) Multiple uterine leiomyomas; (3) (Cervical) HSIL (CIN Grade II); and (4) Postoperative right ureteral stent placement. The patient is currently receiving TC regimen chemotherapy.

5. Exploration

To further clarify whether there is a relationship between cervical HSIL and ovarian poorly differentiated carcinoma, a consultation was conducted at Peking University Third Hospital. The immunohistochemistry results of the cervical biopsy tissue: P16 (+), Ki-67 (2/3+ in the squamous epithelium); molecular pathology results: HPV RNAscope HR18 multiple subtypes (+).Total hysterectomy + left adnexa: (1) Multiple uterine leiomyomas; atrophic endometrium; chronic cervicitis, focal HSIL (CIN Grade 2). (2) "Ureteral surface mass" showed tumor cell infiltration. "Intestinal surface mass" showed a small number of tumor cells in the fibrous tissue. The uterine serosal surface, left adnexa, and "left rectal sulcus peritoneum, right rectal sulcus peritoneum, uterine artery" showed no tumors. Immunohistochemistry results: P16 (-), Ki-67 (2/3+ in the squamous epithelium). DF25-0517422 section: (Right adnexa) malignant tumor, immunohistochemistry results: P53 (missense mutant expression), WT-1 (+), BAP1 (+), Calretinin (-), HBME-1 (-), D2-40 (-), MTAP (weak +), CK5/6 (+), TRPS1 (scattered +), NTRKpan (-), NUT (-), Inhibinα (-), Rb (+), MLH1 (+), PMS2 (+), MSH2 (+), MSH6 (+), P40 (partial +), P63 (partial +), P16 (-), HER-2 (0); Ki-67 (2/3+ in the squamous epithelium).

In Situ Hybridization: HPV RNAscope HR18 multiple subtypes (+). Molecular pathology results: NGS1021+oncofusion gene detection (TP53 gene variation and FGFR-REEP3 fusion detected in the tumor; MSS; TMB-L: 2.25 Muts/Mb, 37%); oncofusion gene detection: no gene rearrangement detected in the tumor; pathogenic BRCA1 germline gene mutation detected in peripheral blood. Based on the immunohistochemistry and molecular detection results, it is consistent with HPV infection-related poorly differentiated squamous cell carcinoma. Therefore, this patient is considered to have primary HPV infection-related poorly differentiated squamous cell carcinoma of the cervix metastasizing to the right ovary.

6. Discussion

Ovarian metastasis from cervical cancer is not rare clinically, but ovarian metastasis of poorly differentiated squamous cell carcinoma from cervical HSIL has not been reported. Mei Quan et al. [1] showed that the probability of ovarian metastasis from cervical cancer roughly fluctuates between 0.12% and 2.22%, with squamous cell carcinoma having a lower rate than adenocarcinoma. Zhang Shiqian et al. [2] pointed out that a study by the American Gynecological Oncology Group (GOG) found that the ovarian metastasis rate of Stage IB cervical squamous cell carcinoma was 0.5%. Shimada et al. [3] reported a large-sample clinical retrospective study with an ovarian metastasis rate of 1.5% in cervical cancer. Yamamoto et al. [4] reported an ovarian metastasis rate of 2.22%. There are also many reports of ovarian metastasis of cancer cells after ovarian preservation in cervical cancer. Ivanov et al. [5] found that in a survey after ovarian transposition in cervical cancer, ovarian metastasis occurred in 3 cases of squamous cell carcinoma and 3 cases of adenosquamous carcinoma. Among cervical squamous cell carcinoma patients who preserved their ovaries during the initial surgery, Sanjun et al. [6] reported a case of bilateral ovarian metastasis within 1 year after Stage IIB surgery. Piketty et al. [7] reported a case of ovarian metastasis of preserved cancer in a Stage IB cervical adenocarcinoma patient 17 months after surgery.

Metastatic Pathways: Direct spread is the most common in cervical cancer, so metastasis in advanced patients is understandable. When the uterine body is involved, due to the clinical characteristic of infiltrative growth of cervical adenocarcinoma, when the parauterine tissues are directly involved, cancer cells can directly invade the ovarian tissue or reach the ovary through the blood vessels and lymphatic vessels of the cardinal and broad ligaments. Nakanishi et al. [8] believed that in cervical cancer patients, the larger the tumor diameter, especially when it exceeds 3cm, the higher the chance of ovarian tissue involvement. Wen Qiang et

al. [9] found that the probability of ovarian metastasis in cervical minimal deviation adenocarcinoma reached 30%, significantly higher than other tissue cell types. Regarding the ovarian metastasis rates of cervical cancer patients in Stages IB, IA, and IIB, Landoni et al. [10] reported rates of 0.83%, 1.14%, and 3.33%, respectively, fully indicating a positive correlation between tumor stage and ovarian metastasis rate. How do early patients metastasize? And the patient's cervix only showed HSIL (Grade II). Samaila et al. [11] believed that there is a significant positive correlation between vascular invasion of cervical cancer cells and ovarian metastasis, speculating that cervical cancer cells can invade the ovary through blood transportation. The reason why only HSIL without invasive squamous cell carcinoma was detected in the cervical site in this case may be: (1) Limited by the amount of tissue sampled, invasive cancer was not observed; (2) The invasive cancer focus was very small and metastasized into the bloodstream at an early stage. The latest tumor metastasis theory suggests that, in individual cases, metastasis can occur when the maximum diameter of the primary lesion is less than 1mm. Moreover, HSIL lesions (positive for high-risk HPV E6/E7 mRNA) were detected in both the biopsy and total resection specimens at the cervical site. High-risk HPV E6/E7 mRNA was detected in the poorly differentiated squamous cell carcinoma of the ovary using RNAscope technology, along with the expression of squamous differentiation markers such as CK5/6, P40, and P63, supporting that the ovarian metastasis originated from primary cervical squamous cell carcinoma.

Treatment and Prognosis: Treatment should consider both the primary cervical cancer and the metastatic lesions. For cervical cancer patients who undergo initial surgical treatment and subsequently develop ovarian metastasis, radiotherapy and chemotherapy are mainly recommended, with surgery as an adjunct. This patient is receiving TC regimen chemotherapy combined with radiotherapy, following the treatment principles for advanced cervical cancer. Patients with ovarian metastasis from cervical cancer generally have a poor prognosis. A study in the United States showed that the 5-year survival rates of cervical cancer patients in China, Japan, and Europe were 79%, 72%, and 62%, respectively. During the same period, similar to the study by Mei Quan et al. [1], Shimada et al. [3] reported a 5-year survival rate of 39.44% for cervical cancer patients with ovarian metastasis, and Ma Shaokang et al. [12] reported only 17.65%. It can be considered that ovarian metastasis is one of the factors for a poor prognosis in cervical cancer.

7. Conclusion

Squamous cell carcinoma, neuroendocrine carcinoma, and adenocarcinoma of the cervix have all been reported to metastasize to the ovary. Although many patients have a known history of cervical canal tumors before the appearance of ovarian tumors, it is rare for ovarian masses to occur before cervical cancer. The difficulty in recognizing the potentially invasive behavior of certain clinically occult or microinvasive tumors makes diagnosis more challenging. Zhu Sijing et al. [13] found that in postmenopausal women, cervical atrophy and inward migration of the squamocolumnar junction make it difficult to expose the high-incidence area of cervical lesions, making cytological examination more difficult to obtain and limiting the amount of tissue sampled, thus restricting a clear diagnosis. For ovarian squamous cell carcinoma, it is crucial to determine whether it is primary or metastatic and to exclude primary cervical metastatic SCC, as this plays a key role in the subsequent treatment of patients. Recently, Tamura K et al. [14] found that serum lymphocyte chemokine (XCL1) has a certain value in differentiating the tissue origin of ovarian squamous cell carcinoma. XCL1 is specifically overexpressed in primary ovarian squamous cell carcinoma and not expressed in metastatic ovarian squamous cell carcinoma. For postmenopausal patients with HR-HPV infection, active and effective intervention should be implemented to avoid disease progression and delayed treatment.

Disclosure statement

The authors declare no conflict of interest.

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