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Case Report

Peutz Jeghers syndrome accompanied with cervical gastric adenocarcinoma and extensive metastasis: a case report

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Abstract: Female pathological tumors are easily misdiagnosed and missed in clinical practice. Especially in patients with Peutz-Jeghers syndrome (PJS) who often have a variety of rare types of gynecological tumors. We reported a patient with a case of PJS with a lower abdominal mass as the clinical manifestation. Physical and auxiliary examinations showed a large pelvic and abdominal mass. According to the patient's PJS history, gastric adenocarcinoma (GAC) was diagnosed after timely cervical biopsy. The patient underwent abdominal and pelvic mass resection and extensive hysterectomy. The tumor extensively disseminated to the bilateral ovaries, endometrium, fallopian tubes and pelvis. The cyclin-dependent kinase inhibitor 2A gene mutation was demonstrated in cervical GAC samples using next-generation sequencing. We summarized the literature on PJS accompanied by GAC with metastases to bilateral ovaries and analyzed the clinical characteristics of female patients with PJS combined with multiple gynecological tumors. Being aware of the PJS history of the patient is helpful for the standardized diagnosis and treatment of PJS-related gynecological tumors.

Keywords: Peutz-Jeghers syndrome, cervical gastric-type adenocarcinoma, extensive metastases, next generation sequencing, STK11, CDKN2A

Introduction

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant genetic disease characterized by mucocutaneous melanin pigmentation and gastrointestinal polyposis. It was first reported in 1921 and 1949 by Peutz and Jeghers, respectively, with an incidence from 1/50,000 to 1/250,000 [1]. Approximately 50% of PJS patients have a family history [2], and the patient is often characterized by mucocutaneous pigmentation and multiple hamartoma polyps in the digestive tract. The pathogenesis of PJS has been confirmed to be mainly related to LKB1/STK11 gene abnormalities [3, 4]. More studies have confirmed that PJS sufferers have an increased risk of malignancy. In addition to the digestive tract, malignant tumors in PJS sufferers are more common in the breast, uterus, ovary and other parts of the body. Tumors associated with the female reproductive system mainly include gastric-type adenocarcinoma (GAC) and sex cord tumors with annular tubules (SCTAT) [1, 5].

GAC is the most common type of non-HPV-associated adenocarcinoma (NHPVA), accounting for approximately 10%-15% of cervical adenocarcinomas [6]. On the one hand, GAC is composed of well-differentiated mucinous adenocarcinoma, with histology similar to gastric glandular epithelium and expression of the gastric mucus marker. On the other hand, some benign hyperplastic endocervical glands might be over diagnosed as GAC. Therefore, there is the possibility of underdiagnosis and misdiagnosis of GAC in clinical practice. In recent years, with the wide application of next-generation sequencing (NGS), corresponding genetic abnormalities have also been found in GAC. We report a rare case of PJS accompanied by GAC spreading to the bilateral ovaries, endometri-

um, fallopian tubes and pelvic cavity. To further explore the pathogenesis of gynecologic malignancies in PJS patients, we performed NGS detection of the tumor susceptibility gene in our case.

Case report

Clinical details

In April 2020, a 32-year-old Chinese female presented with a mass in her lower abdomen that was present for one week. The patient had palpated a lower abdominal mass with abdominal distension without discomforts such as abdominal pain, anorexia, frequent urination, urgent urination, abnormal vaginal bleeding, or watery discharge. The patient had scattered pigmented spots at the ends of her limbs and lips that appeared in her childhood. She was diagnosed with PJS after gastrointestinal polypectomy 2 years ago. Serum tumor markers were detected as follows: CA199 as 255.3 U/ml, CA125 as 34.9 U/ml, CEA as 2.9 ng/ml and AFP as 1.4 ng/ml. Enhanced CT scan of the whole abdomen showed huge cystic space occupying lesions in the abdomen and pelvis with unclear boundary with bilateral ovaries, with the size of 17.3 cm × 15.5 cm × 9.6 cm and 11.3 cm × 11.1 cm × 8.6 cm, respectively (**Figure 1A**, **1B**).

Because the patient had a history of PJS, a cervical biopsy was performed and she was diagnosed as having GAC. The patient underwent abdominal and pelvic mass resection and extensive hysterectomy. During the operation, it was found that the abdominal cavity was filled with a light yellow viscous liquid, with a volume of approximately 5000 milliliters. A separated cystic solid mass of approximately 25 cm × 20 cm × 18 cm could be seen in the right ovary and jelly-like material was seen inside. A 12 cm × 10 cm × 10 cm septal cystic solid mass was seen in the left ovary. A 6 cm × 6 cm × 5 cm solid mass was found at the right sacral ligament. Intraoperative pathological frozen section examination of ovary and sacral ligament nodules confirmed adenocarcinoma infiltration.

Pathological findings

Macroscopically, the cervix was thickened in a barrel shape with a cribriform section and mucus inside (**Figure 1C**). The surface of the bilateral ovarian tumors was smooth, and the sections were multilocular cystic (**Figure 1D**). Jelly like substances were seen inside, with no normal residual ovarian tissue.

Histologically, previous ileal polyps could be seen with broad branched smooth muscle bundles inserted into the mucosal layer surrounded by normal crypt glands (**Figure 2A**). Bilateral ovarian tumors were lined with a single layer of high columnar mucinous epithelium with papillary growth into the cavity (**Figure 2B**). The lined epithelium had morphological characteristics similar to those of gastric mucinous epithelium with mild atypia. In some areas, enlarged nuclei, vesicular nucleoli and mitotic figures were easily seen, and small infiltrating glands could be seen in the deeper layer of the stroma. Immunohistochemical staining showed that the ovarian tumor expressed CK7, Pax-8, MUC-6, and MUC-5, while CK20, ER, PR, MUC-2, Pax-2, CDX2, SATB2 and CA125 were all negative (**Figure 3A-C**). The Ki67 index was approximately 20%. Cervical tumor cells also showed mild atypia. Tumorous glands similar to normal cervical endometrium infiltrated into the deeper layer of cervical stroma, without obvious stromal reaction (**Figure 2C**). The tumor cells were highly columnar, with the nucleus located at the base, and showed a prominent cell border. Goblet intestinal epithelium was also dispersed throughout the lesion. The immunophenotype of the cervical tumor was consistent with that of the ovarian tumor (**Figure 3D-F**). The tumor extended into the endometrial cavity, partially replaced the normal endometrium (**Figure 2D**), and spread to the mucosa and serosa of the fallopian tube. Adenocarcinoma with morphology similar to that of cervical lesions was found in sacral ligament nodules.

The patient had no PJS family history. We detected tumor susceptibility genes in her GAC tissue, screening the whole exon region of 310 genes and 210 gene hot spot mutation regions by probe hybridization and high-throughput sequencing. The results showed a p.s8fs frameshift mutation in exon 1 of the cyclin-dependent kinase inhibitor 2A gene (CDKN2A).

Treatment and follow-up

The patient was diagnosed as having stage IV cervical GAC with extensive involvement

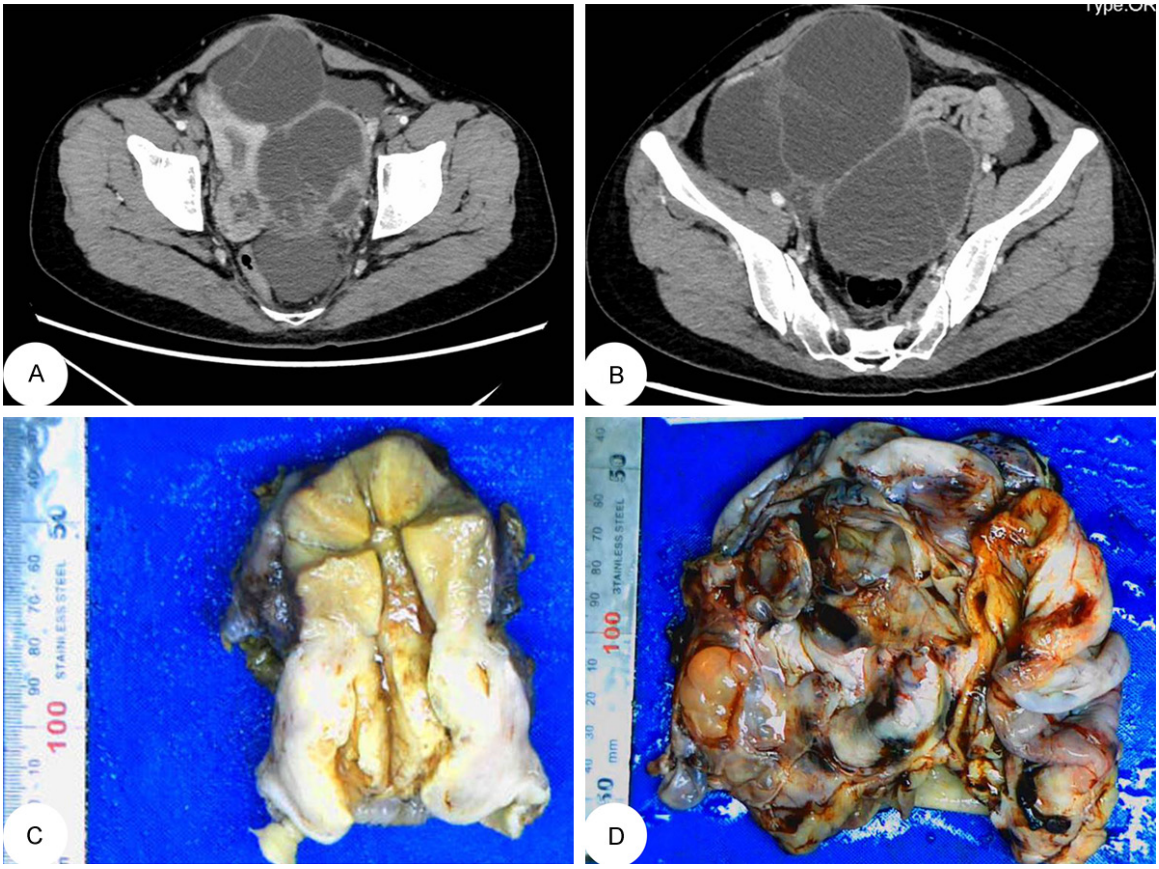

Figure 1. A, B: A huge cystic solid mass is seen in the pelvic cavity, with septal and solid components, pushing the uterus to the right; C: The cervix was thickened in a barrel shape; D: The surface of the ovarian tumor was smooth, and the cut surface was multilocular cystic.

of bilateral ovaries, endometrium, fallopian tubes and pelvis, followed by paclitaxel + DDP + bevacizumab chemotherapy for six cycles (September 26, 2020). On April 16, 2021, PET-CT showed multiple abdominal and pelvic seeding metastases (perihepatic, omentum, pelvic peritoneum), and the patient received TOPO + DDP + bevacizumab chemotherapy for four cycles. The patient died 4 months later (August 22, 2021).

Discussion

We report a rare case of cervical GAC of a PJS patient with extensive involvement of the endometrium, bilateral appendages, and pelvis. The incidence of GAC in female patients with PJS is approximately 15%-30% [1], while approximately 10% of GAC cases are accompanied by PJS [7]. GAS is associated with somatic and germline STK11 mutations and TP53 mutations [8]. Kuragaki's study showed STK11 gene mutation in 6 (55%) of 11 patients with GAC [9]. However, STK11/LKB1 somatic mutations were not detected in 13 cases of sporadic ovarian SCTAT or cervical GAC [10]. Yang-Yang Feng presented the first case of bilateral PJS-associated SCTAT combined with unilateral AGCT that had STK11 germline mutation [11]. Thus, the tumorigenic role of STK11 abnormalities in PJS-related gynecological tumors remains to be further confirmed. However, if the mutation of STK11 is detected in the GAC, it suggests that clinicians should further screen patients for the possibility of PJS. Jung et al detected KRAS, TP53, NF1, CDKN2A, STK11 and ARID1A gene abnormalities in 8 cases of cervical NHPVA using RNA-NGS, while KRAS, PIK3CA, TP53, and BRCA2 gene abnormalities were detected in HPVA [12], suggesting that these two types of adenocarcinoma have different pathogenesis. Garg et al also detected 92 variants in 14 cervical GAC samples using NGS [13], of which TP53 was the most frequently mutated gene, followed by

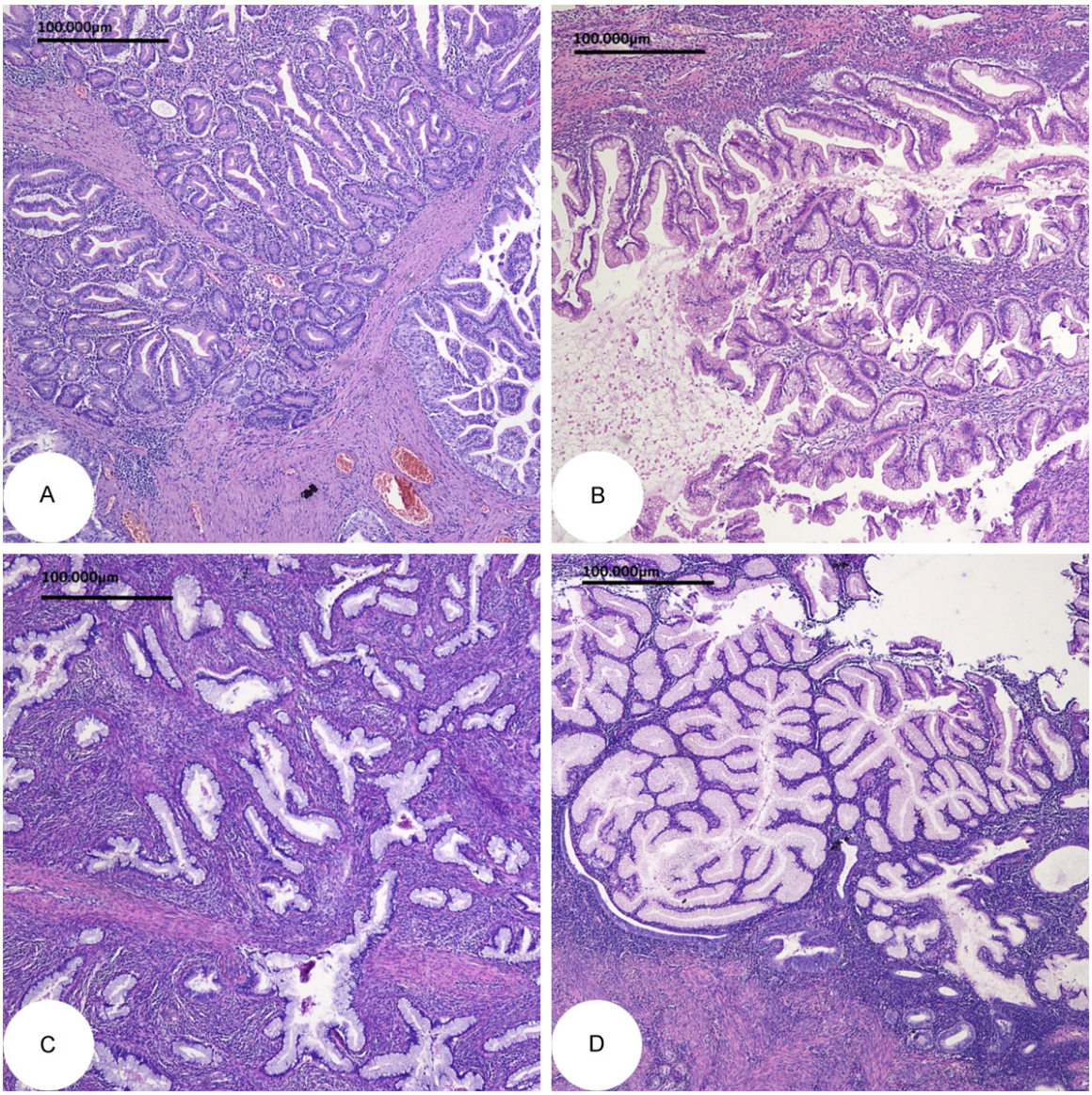

Figure 2. Histological findings. (A) Ileal Peutz-Jegher polyp showed villous architecture and arborizing smooth muscle cores; (B) Ovarian tumor was lined with a single layer of high columnar mucinous epithelium with papillary growth into the cavity; (C) In cervical gastric adenocarcinoma, tumorous glands with mild atypia could be seen to infiltrate into the deeper layer of cervical stroma, without obvious stromal reaction; (D) The tumor extended into the endometrial cavity, partially replaced the normal endometrium (Hematoxylin and Eosin staining. Magnification: A-D, ×100).

MSH6, CDKN2A/B, POLE, SLX4, ARID1A, STK11, BRCA2, MSH2 ARID1A and others [14, 15]. The NGS results of cervical GAC tissue in our case also confirmed the mutation of the CDKN2A gene, which was helpful to confirm the diagnosis of GAC.

GAC is the most common type of cervical adenocarcinoma and accounts for around 10%-20% of all cervical adenocarcinoma as first described by Kojima [16]. The typical clinical manifestations of GAC are watery leucorrhea, irregular vaginal bleeding and barrel cervix. Morphologically, it is similar to cholangiopancreatic adenocarcinoma and has similar immunohistochemical characteristics. Microscopically, the tumor is well-differentiated and shows gastric mucus differentiation, which is often difficult to distinguish from normal cervical glands. However, the glands are disorderly and abnormally distributed and can grow infiltrating into the deeper stroma of the cervix. Up

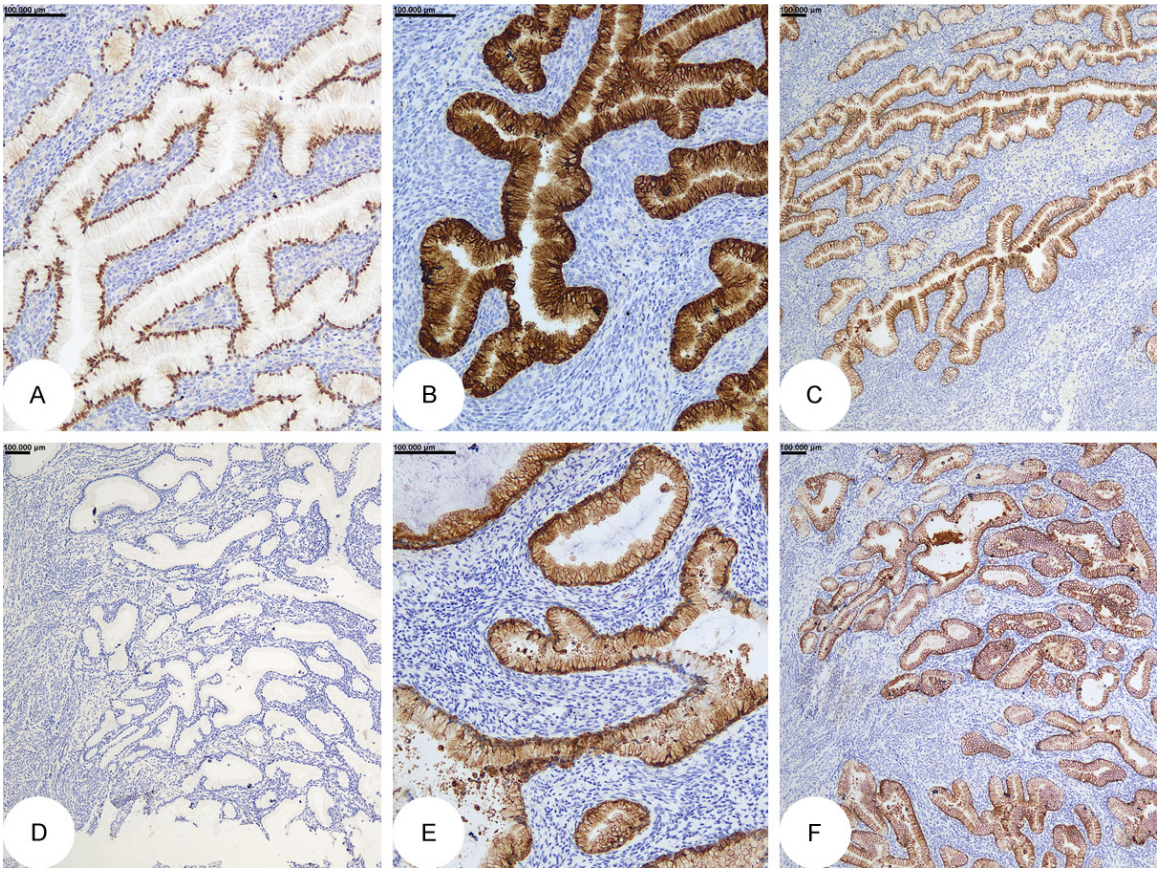

Figure 3. Immunohistochemistry (IHC). A: PAX8 was positive in Ovarian adenocarcinoma (×100); B: MUC6 was positive in Ovarian adenocarcinoma (×100); C: CK7 was positive in Ovarian adenocarcinoma (×40); D: PAX2 was negative in cervix adenocarcinoma (×40); E: MUC6 was positive in cervix adenocarcinoma (×100); F: CK7 was positive in cervix adenocarcinoma (×40).

to 50% of GAC cases exhibit p53 mutant expression in immunophenotype [16]. Usually, p16 expression is negative or shows patchy spot positivity, and only a small number can exhibit diffuse and strong positive expression. Pax-2, ER and PR are usually negative [17]. Nearly 68%-80% of GAC expressed Pax-8 and the gastric mucin markers MUC6 and HIK1083 [18, 19]. In addition, approximately 50% of GAC can express CK20 and CDX2. Up to 90% of GAC can express HNF1B but rarely express NapsinA, which can be differentiated from clear cell carcinoma [8]. GAC is highly invasive, progresses rapidly, and has a poor prognosis. Most patients are in an advanced stage at the time of diagnosis and are resistant to conventional chemotherapy. Surgical treatment is the most appropriate choice [20]. Compared with cervical HPVA, the prognosis of GAC is worse, with a 5-year survival rate of 30%-42%, while that of HPVA is approximately 74%-91% [1, 7].

PJS accompanied by GAC that spread to bilateral ovaries is very rare. At present, only four similar cases have been reported in the literature [5, 21-23]. In our case, the symptoms of GAC were insidious, and there were no symptoms of vaginal watery discharge or bleeding. Initially, the patient went to the hospital complaint with abdominal pain, and an auxiliary examination revealed masses in the bilateral ovaries. Ovarian tumors associated with PJS are mostly unilateral SCTAT or mucinous cystadenoma. Therefore, we decided to determine whether there were cervical lesions related to PJS after learning about the patient's PJS history. The diagnosis of GAC was confirmed after the subsequent cervical biopsy. Intraoperative frozen examination and postoperative immunohistochemistry confirmed that bilateral ovarian and sacral ligament nodules were metastatic adenocarcinomas derived from the cervical GAC, providing accurate clinical stage and sub-

sequent treatment options for clinicians and the patient.

In summary, we report a case of PJS accompanied by GAC with an extensive invasion of the cervix and pelvic endometrium. Because of the strong correlation between PJS and cervical or ovarian tumors, we suggest that patients with a history of PJS and their family members should pay attention to the screening of gynecological diseases. American ACG guidelines suggest that female PJS patients and their immediate family relatives should have a pelvic examination every year after the age of 25 to exclude lesions of the uterus and ovary [24]. Regular cervical cytology, pelvic ultrasound, pelvic CT, and MRI are also necessary. Cervical biopsy or cervical conization should be done promptly for patients with abnormal cervical lesions found in the auxiliary examination mentioned above to clarify the nature of the lesions. Early diagnosis and timely personalized treatment are closely related to the prognosis of the disease. Multiple gene detection should be considered for patients with PJS complicated with gynecological tumors when possible, which is helpful in evaluating the disease and investigating the pathogenesis.

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The patient provided her written informed consent to participate in our study.

Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Abbreviations

PJS, Peutz-Jeghers syndrome; GAC, Gastric-type adenocarcinoma; SCTAT, Sex cord tumors with annular tubules; NHPVA, Non-HPV-associated adenocarcinoma; NGS, Next-generation sequencing; CDKN2A, Cyclin-dependent kinase inhibitor 2A gene; IHC, immunohistochemistry.

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