CASE REPORT
Gastric-type mucinous adenocarcinoma of the cervix in a woman with Peutz-Jeghers syndrome: a case report

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ABSTRACT
Background: Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by a predisposition to the development of multiple neoplasms. Gastric-type mucinous adenocarcinoma (GAS), a new variant of carcinoma of the cervix according to 2014 WHO classification, is less common compared with squamous cell carcinoma, is more aggressive and has a lower 5-year survival rate compared with the usual-type endocervical adenocarcinoma, and is also unrelated to human papillomavirus (HPV) infection.

Case summary: We herein present the case of a 32-year-old patient with PJS who was diagnosed with GAS of the cervix. The patient was not sexually active and had been diagnosed with PJS at 2 years of age. A tumor of 6 cm was found on the cervix and was diagnosed as GAS of clinical-stage IB3. The patient was treated with intra-arterial chemotherapy for one course, followed by radical surgery and then systematic chemotherapy.

Conclusion: The present case highlights the need for more thorough cancer screening for patients with PJS, as this disorder is rare and is associated with a high risk of malignancies. Young patients with PJS, including those who are not sexually active, who present with watery vaginal discharge or bleeding should be screened for cervical carcinoma, even if the cytological results or HPV tests are negative.

Abbreviations: PJS: Peutz-Jeghers syndrome; GAS: gastric-type mucinous adenocarcinoma; UEA: usual-type endocervical adenocarcinoma; HPV: human papillomavirus; MRI: magnetic resonance imaging; CA125: carbohydrate antigen125; CA199: carbohydrate antigen199; CA153: carbohydrate antigen153; CA724: carbohydrate antigen724; SCTAT: sex cord tumour with annular tubules

Introduction
Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder, which is characterized by mucocutaneous pigmentation, multiple hamartomatous polyps in the gastrointestinal tract and predisposition to the development of certain neoplasms [1]. The incidence of PJS has been estimated to be between 1 in 50,000 and 1 in 200,000 live births [1,2]. Previous studies [3,4] reported that 11–17% of women with PJS are diagnosed with gastric-type mucinous adenocarcinoma (GAS) of the cervix.

Cervical adenocarcinoma is less common compared with cervical squamous cell carcinoma, but its incidence has been increasing in recent years, particularly among young women, and is currently estimated to account for up to 10–25% of all invasive cervical carcinomas [5]. GAS is a novel variant of endocervical mucinous adenocarcinoma according to 2014 WHO classification [6]. It represents a more aggressive disease and a poorer prognosis than the usual-type endocervical adenocarcinoma (UEA) [7,8]. We herein report a case of adenocarcinoma of the cervix, diagnosed by cervical biopsy in a woman with PJS, which was eventually histopathologically confirmed to be GAS following radical surgery.

Case report
The present study was approved by the Institutional Review Board of the International Peace Maternity and Child Health Hospital (Shanghai, China). A 32-year-old woman who was not sexually active presented in August 2020 with a history of recurrent watery vaginal discharge for >6 months and prolonged menstrual periods over
the preceding 3 months. Pelvic magnetic resonance imaging (MRI) revealed a cervical mass of 5.8 × 5.6 × 7.6 cm, while enlarged lymph nodes were not identified (Figure 1). The patient had been diagnosed with PJS when she was admitted to a tertiary hospital for mucocutaneous pigmentation over the lips at 2 months of age. She had a history of colon polyps resection by colonoscopy when she was 12 years old, after which time she underwent routine colonoscopy and biopsy annually. In 2002, when the patient was 14 years old, she underwent emergency surgery for bowel obstruction. In 2018, she had surgery for the removal of a right breast tumor, which was confirmed on pathological examination as a benign fibroma. No other family members had been diagnosed with PJS.

On physical examination, the patient displayed mucocutaneous pigmentation over the lips, particularly the lower lip, and in the nostrils (Figure 2). Laboratory tests revealed no abnormal blood, urine or stool findings. The human papillomavirus (HPV) test was negative. The levels of tumor markers, including carbohydrate antigen (CA)125, CA199, squamous cell carcinoma antigen, CA153, CA724, carcinoembryonic antigen, α-fetoprotein and human epididymis protein 4, were within the normal range.

A gynecological examination was performed under anesthesia. A tumor ~6 cm was found on the cervix, whereas the vagina was not invaded and the parametrium was soft on physical examination. A biopsy was performed and paraffin section pathology revealed moderately differentiated GAS of the cervix.

In accordance with the 2018 International Federation of Gynecology and Obstetrics criteria(9), the final diagnosis was GAS of the cervix of clinical-stage IB3. The patient was administered intra-arterial chemotherapy for one course [10,11], consisting of intravenous Taxol (135 mg/m²) and bilateral uterine intra-arterial cisplatin (80 mg/m²). MRI was performed 2 weeks later for tumor assessment. On the MRI, the tumor had shrunk to ~4 cm, and some dartoid tissue was discharged from the vagina 1 week after the intra-arterial chemotherapy, as reported by the patient.

Eventually, the patient underwent a laparoscopic radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node dissection 3 weeks after the artery intervention chemotherapy. The final histopathological analysis of the surgical specimen confirmed the diagnosis of moderately differentiated cervical GAS (Figure 3). No myometrial invasion or metastasis to pelvic lymph nodes was observed. There was also no lymphovascular space invasion and the vaginal resection margins were clear. The results of the immunohistochemical examination were as follows: Mucin (MUC6⁺, MUC2⁻, patchy P16 positivity, ER⁻ and PR⁻ (Figure 4(A–E)). A gene test was also performed and a mutation of the serine/threonine kinase (STK)11 gene was confirmed. The patient received adjuvant chemoradiotherapy after the radical surgery, comprising intravenous Taxol (135 mg/m² every 21 days) and carboplatin (area under the plasma drug concentration-time curve = 5 every 21 days) and external irradiation 25 times. The patient was scheduled to receive 6 courses of intravenous chemotherapy in total,
which had already been completed at the time this article was drafted, and the treatment was well-tolerated. The follow-up was scheduled every 3 months in the first 3 years, every 6 months over the next 2 years, and annually thereafter. The last visit was on April 28th, 2021, and the patient was in good status and the examination revealed no significance.

Discussion

PJS is a rare clinical syndrome, occurring as an autosomal dominant inherited disorder, which is characterized by gastrointestinal (commonly small-bowel) hamartomatous polyposis, mucocutaneous melanin pigmentation and predisposition to certain neoplasms [12]. Drs Jan Peutz and Harold Jeghers were the first to systematically describe the inherited form of PJS in patients with gastrointestinal hamartomatous polyps and mucocutaneous melanin pigmentation, which are the characteristic features distinguishing PJS from other gastrointestinal polyposis syndromes [13,14]. The incidence of PJS is estimated to range between 1 in 50,000 and 1 in 200,000 individuals. According to a European consensus statement [15], PJS is diagnosed based on the following clinical criteria: Two or more histologically confirmed PJS-type hamartomatous polyps; any number of PJS-type polyps detected in one individual who has a family history of PJS in at least one close relative; characteristic mucocutaneous pigmentation in an individual who has a family history of PJS in at least one close relative; any number of PJS-type polyps in an individual who also has characteristic mucocutaneous pigmentation.

PJS may be defined by a mutation of the STK11 gene (chromosome 19p13.3). STK11 encodes a serine/threonine kinase, which participates in cell metabolism and proliferation [16]. In ~94% of patients with PJS [17,18], a germline mutation of STK11 was detected. In the present case, the patient was found to harbor an STK11 mutation on chromosome 19 in exon 4. A number of mutations, including deletion, insertion and inversion mutations, have been reported to date in almost every coding exon, but mainly in exons 1, 5, 6 and 7 [19,20]. However, the reports on genotype-phenotype correlation associated with STK11 pathogenic variants are conflicting. The major source of morbidity and mortality among young patients is intestinal intussusception. Another cause is the increased cumulative risk of cancer. The most common types of cancer associated with PJS are breast and colon cancer, with the cumulative risk being >30%, while the respective risks in the general population are 12.4 and 5% [1]. The risk of cervical cancer in patients with PJS is 10%, while in the general population it is <1%. The PJS-specific cancer surveillance guidelines are summarized in Table 1 [1].

There are two characteristic gynecological tumors in patients with PJS [21]: GAS of the endocervix and ovarian sex cord tumor with annular tubules (SCTAT). Occasionally, ovarian oxyphilic Sertoli cell tumors may develop in patients with PJS [22]. A previous meta-analysis reported the cumulative risk of cervical cancer in patients with PJS to be ~9%, with the mean age at diagnosis in the third decade [21]. Adenoma malignum (also known as minimal deviation adenocarcinoma) is commonly encountered, which was categorized as a well-differentiated form of GAS in the 2014 WHO classification system. On the other hand, among patients who are diagnosed with GAS, 11–17% have PJS [4,23], while ovarian tumors, most of which are SCTAT [24], occur in ~21% of patients with PJS.

The histological criteria [25,26] for the diagnosis of GAS are as follows: (i) Clear or pale eosinophilic cytoplasm, (ii) voluminous cytoplasm and (iii) distinct cell borders. The characteristic immunophenotype of GAS is the presence of pyloric gland mucin, which is reflected by positive MUC6 and HIK1083 staining. Both MUC6 and HIK1083 mark pyloric gland mucin of the stomach, and they are positive in most cases of GAS and lobular endocervical glandular hyperplasia, but not in normal endocervix or UEA [8,12]. However, as MUC6 is
more widely available than HIK1083, only MUC6 staining was performed in the present case. As GAS is unrelated to high-risk HPV 16 [8,27–29], p16 staining is usually patchy or negative. The lack of estrogen receptors is observed in most GAS cases, such as the present case.

The presenting sign of GAS is often mucoid or watery vaginal discharge or vaginal bleeding, and widespread involvement and advanced stage are commonly seen when the initial diagnosis is established. Ovarian metastases are also not uncommon. The biological behavior of GAS is more aggressive compared with UEA, and the 5-year survival rate is less than half of that for UEA [21,30]. As patients with GAS usually have the advanced-stage disease and widespread organ involvement at diagnosis, their prognosis is markedly worse compared with that of patients with UEA. In the present case, bi-oophorectomy was suggested and finally performed after obtaining the patient’s consent. Furthermore, according to the 2018 LACC clinical trial [31], the surgical procedure of laparoscopic radical hysterectomy was improved. During surgery, a tape was used for uterine manipulation.

Figure 4. Immunohistochemical staining was (A) positive for MUC6, a marker of pyloric gland mucin, and (B) negative for MUC2. (C) Patchy staining was observed for P16. Immunohistochemical staining was negative for (D) estrogen receptor and (E) progesterone receptor. MUC, mucin.
rather than a cup-type uterine trans-cervical manipulator; in addition, colpotomy was performed transvaginally, and the uterus was removed through the vagina with the cervix encased in the dissected vaginal wall.

Due to the high risk of malignancy associated with PJS, a more thorough cancer screening has been recommended. First, annual pelvic ultrasound and cervical screening tests have been recommended for cancer screening in women with PJS aged >18 years [1,12,21]. Since cytological or HPV tests are usually negative in GAS, the presence of an enlarged cervix with multiple cysts or persistent vaginal discharge or bleeding in a patient with PJS warrants a cervical biopsy, even if the patient is not sexually active.

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Ethics approval and consent to participate

The Institutional Review Board (International Peace Maternity and Child Health Hospital) approved this work.

Consent for publication

Informed consent for publication of clinical data/details/images was obtained from the patient. A copy of consent is available for review by the Editor of this journal.

Author contributions

TT: writing of the manuscript. FQ: providing the case details. SS: providing the case details. LYH: writing and editing of the manuscript. WYD: editing of the manuscript. The authors read and approved the final manuscript.

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Data availability statement

There is no dataset as this is a case report. Data/details of the patient available upon request.

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Table 1. Screening and surveillance guidelines for Peutz-Jeghers syndrome.

| Site           | Procedure                                      | Age at initial screening (yr) | Interval         |
|----------------|-----------------------------------------------|-------------------------------|------------------|
| Stomach        | Upper endoscopy                               | 8, 18*                        | 3 yrs*           |
| Small intestine| Capsule endoscopy or MRE                      | 8, 18*                        | 3 yrs*           |
| Large intestine| Colonoscopy                                    | 8, 18*                        | 3 yrs*           |
| Breast         | Breast self-examination                        | 18                            | 1x/mo            |
|                | Clinical breast exam                           |                               | 6 mos            |
|                | Breast MRI or digital mammography             | 25                            | 1 yr             |
| Ovary, cervix, uterus | Transvaginal ultrasound & serum CA 125; pelvic exam w/pap smear | 18–20                       | 1 yr             |
| Pancreas       | MRI-MRCP or endoscopic ultrasound            | 30                            | 1–2 yrs          |
| Testes         | Testicular exam; ultrasound if symptomatic or abnormality on exam | Birth to teen yrs            | 1 yr             |

MRCP: magnetic resonance cholangiopancreatography; MRE: magnetic resonance enterography.
*If significant polyps are present at baseline, repeat upper endoscopy/colonoscopy every three years. If no significant polyps are present at baseline, repeat at age 18 years and then every three years.
*CT enterography may be used as an alternative. The use of MR enterography allows for simultaneous surveillance for pancreatic cancer.
*If few or no polyps at baseline, repeat at age 18 years.
*Digital mammography if MRI not available.
*Discuss prophylactic mastectomy.
*Discuss prophylactic hysterectomy and oophorectomy.
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