Gastric-type mucinous adenocarcinoma of the cervix in a woman with Peutz-Jeghers syndrome

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Case report

Keywords: Peutz-Jeghers syndrome, gastric-type adenocarcinoma, cervix, HPV

Posted Date: April 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-150876/v2

Abstract

Background: Peutz-Jeghers syndrome(PJS) is a very rare autosomal dominant disorder with predisposition to multiple neoplasms. Gastric-type adenocarcinoma (GAS) is a less common carcinoma of the cervix than squamous cell carcinoma, which is more aggressive and has lower 5 year survival rate than usual type endocervical adenocarcinoma (ECA), and unrelated to human papilloma virus(HPV) infection as well. We present a 32 year-old patient with Peutz-Jeghers syndrome who was found to have gastric-type adenocarcinoma of the cervix.

Case presentation: A 32-year-old woman without sexual life ever who was diagnosed Peutz-Jeghers syndrome when she was two years old presented with watery discharge for more than 6 months. A tumor around 6cm was found on the cervix and she was diagnosed gastric-type mucinous adenocarcinoma of the cervix clinical stage IB3. She was treated with artery intervention chemotherapy for one course followed by radical surgery and then systematic chemotherapy.

Conclusions: The case suggests more thorough cancer screening for patients with PJS as the disorder is rare and has high risk of malignancies. Young patients with Peutz-Jeghers syndrome, including those without sexual life, who have watery discharge or bleeding should be screened for cervical carcinoma even if cytologic results or human papilloma virus (HPV) is negative.

Backgroud

Peutz-Jeghers syndrome(PJS) is a rare autosomal dominant disorder,which is characterized by mucocutaneous pigmentation, multiple hamartomatous polyps in the gastrointestinal tracts and predisposition to certain neoplasm[1]. The incidence of PJS was estimated from 1 in 50,000 to 1 in 200,000 live births[1,2]. Previous reports[3,4] shows that 11–17% of women with Peutz-Jeghers syndrome are found to have gastric-type adenocarcinoma (GAS). We report a case of adenocarcinoma of the cervix, diagnosed by cervical biopsy in a woman with Peutz-Jeghers syndrome, which was eventually histo-pathologically confirmed to be GAS after radical surgery.

Cervical adenocarcinoma is less common than cervical squamous cell carcinoma, but the incidence of cervical adenocarcinoma has been increasing in the recent years, especially in young women. It is estimated to account for up to 10%-25% of all invasive cervical carcinomas[5]. Gastric-type adenocarcinoma (GAS) is a novel variant of endocervical mucinous adenocarcinoma according to the 2014 WHO classification[6]. It represents more aggressive disease and poorer prognosis than the usual-type endocervical adenocarcinoma (UEA)[7,8].

Case Presentation

The institutional review board (International Peace Maternity and Child Health Hospital) approved this work. A 32-year-old woman without sexual life ever presented with a history of recurrent watery vaginal

discharge for more than 6 months and prolonged menstrual periods over the preceding 3 months in August 2020. Pelvic magnetic resonance imaging (MRI) revealed a cervical mass 5.8*5.6*7.6cm while enlarged lymph nodes were not seen (Fig. 1A and 1B). The patient was diagnosed Peutz-Jeghers syndrome at 2 months old at a tertiary hospital for mucocutaneous pigmentations over the lips. She had a history of colon polyps resection by colonoscopy when she was 12 years old and since then had colonoscopy and biopsy every year. In 2002 when she was 14 years old, she had an emergent surgery for bowl obstruction. In 2018 she had a surgery for breast tumor and pathology confirmed benign. No other family members were found with Peutz-Jeghers syndrome.

Physical examination revealed mucocutaneous pigmentations over the lips, especially the lower lip and nostrils (Fig. 2). Laboratory data showed no blood, urine, or stool changes. HPV test was negative. Tumor markers including carbohydrate antigen125(CA125), carbohydrate antigen199(CA199), squamous cell carcinoma antigen(SCC), carbohydrate antigen153(CA153), carbohydrate antigen724(CA724), carcino-embryonic antigen(CEA), alpha fetoprotein(AFP) and human epididymis protein4(HE4) were within normal range.

We proceeded with a gynecological examination under anesthesia. A tumor around 6cm was found on the cervix, vagina and parametrium was not invaded on physical examination. Biopsy was taken and paraffin section pathology diagnosed moderate differentiated gastric-type mucinous adenocarcinoma of the cervix.

In accordance with the latest 2018 International Federation of Gynecology and Obstetrics criteria, gastric-type mucinous adenocarcinoma of the cervix clinical stage IB3 was diagnosed. We gave her artery intervention chemotherapy for one course[9,10] (intravenous taxol 135mg/m^2 and bilateral uterine artery cis-platinum 80mg/m^2). MRI was taken 2 weeks later for tumor assessment. On the second MRI, the tumor shrinked to 4 + cm, and there were some dartoid tissue fell out of vagina one week after the artery intervention chemotherapy told by the patient.

Eventually, the patient underwent laparoscopic radical hysterectomy, bilateral salping-oophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node dissection 3 weeks after the artery intervention chemotherapy. The final histo-pathological analysis of the specimen from radical surgery confirmed moderate differentiated cervical gastric-type mucinous adenocarcinoma (Fig. 3A and Fig. 3B). No myometrial invasion or metastasis to pelvic lymph nodes was observed, no lymphovascular space invasion and clear vaginal resection margins. Immuno-histochemistry shows MUC6(+), MUC2(-), P16 patchy, ER and PR all negative(Fig. 4A-4F). A gene test was also taken and a mutation of STK11 was confirmed. The patient had adjuvant chemoradiation therapy after the radical surgery: intravenous taxol (135mg/m^2 every 21 days) and carboplatin (area under the curve of concentration*time[AUC] = 5 every 21 days). We plan to give her 6 courses of intravenous chemotherapy in total and right now she already has 5 courses and tolerates well.

Discussion And Conclusions

Peutz-Jeghers syndrome (PJS) is a rare clinical syndrome, occurring in autosomal dominant inherited forms, which is characterized by gastrointestinal, commonly small bowel, hamartomatous polyposis, mucocutaneous melanin pigmentation and predisposition to certain neoplasms[11]. Drs Jan Peutz and Harold Jeghers are the first to systematically describe the inherited form of PJS, who both reported patients with gastrointestinal hamartomatous polyps and mucocutaneous melanin pigmentation, which could distinguish PJS from other gastrointestinal polyposis syndromes[12,13]. The incidence of PJS is estimaed about 1 in 50,000 to 200,000 individuals. According to a European consensus statement[14], PJS is diagnosed by the clinical criteria as the following: 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 could be defined by the mutation of STK11 (chromosome 19p13.3). STK11 encodes a serine/threonine kinase which participates in cell metabolism and growth[15]. In about 94% of PJS patients[16,17], germline mutation of STK11 could be detected. In this case, the patient was found STK11 mutation on chromosome 19 in exon 4. Right now a variety of mutations, including deletion, insertion, and inversion mutations, have been reported in almost every coding exon, mainly in exons 1, 5, 6, and 7[18,19]. However, the reports on genotype-phenotype correlation related to STK11 pathogenic variants are conflicting. The major source of morbidity and mortality in young patients is intestinal intussusception. Another is the increased cumulative risk of cancer. The most common are breast and colon, with the cumulative risk being more than 30%, while the general population is 12.4% and 5%, respectively[1]. The risk of cervical cancer in PJS patients is 10%, while the general population is < 1%. PJS-specific cancer surveillance guidelines exist, see table 1[1].

Table 1
Screening and Surveillance Guidelines for Peutz-Jeghers Syndrome

Site	Procedure	Age at Initial Screening(yr)	Interval
Stomach	Upper endoscopy	8, 18[1]	3 yrs[1]
Small intestine	Capsule endoscopy or MRE[2]	8, 18[3]	3 yrs
Large intestine	Colonoscopy	8, 18[1]	3 yrs[1]
Breast	Breast self-examination	18	1x/mo
	Clinical breast exam		6 mos
	Breast MRI or digital mammography[4,5,6]	25	1 yr
Ovary, cervix,uterus	Transvaginal ultrasound & serum CA 125;pelvic exam w/pap smear[6]	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

1. 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.

2. CT enterography may be used as an alternative. The use of MR enterography allows for simultaneous surveillance for pancreatic cancer.

3. If few or no polyps at baseline, repeat at age 18 years.

4. Digital mammography if MRI not available

5. Discuss prophylactic mastectomy.

6. Discuss prophylactic hysterectomy and oophorectomy.

In PJS patients there are two characteristic gynaecological tumours[20]: gastric-type adenocarcinoma of the endocervix (GAS) and ovarian sex cord tumour with annular tubules (SCTAT). Occasionally, ovarian oxyphilic Sertoli cell tumour may occur in PJS patients[21]. One meta-analysis of the literature reported the cumulative risk of cervical cancer in PJS patients to be around 9%, with the mean age at diagnosis in the third decade[20]. Adenoma malignum is commonly seen (also known as minimal deviation adenocarcinoma, MDA), which is now categorized to be a well-differentiated form of GAS in the 2014 World Health Organization(WHO) classification system. On the other hand, among the patients who are diagnosed GAS, about 11–17% have PJS[22,23]. While ovarian tumors, most of which are SCTAT[24], occur in about 21% of PJS patients.

The histological criteria[25,26] for the diagnosis of gastric-type adenocarcinoma is as follows: 1) clear or pale eosinophilic cytoplasm, 2) voluminous cytoplasm, and 3) distinct cell borders. The characteristic immune-phenotype of GAS is the presence of pyloric gland mucin, which means positive MUC6 and HIK1083 staining. Both MUC6 and HIK1083 mark pyloric gland mucin of the stomach, and are positive in most GAS and lobular endocervical glandular hyperplasia(LEGH) but not in normal endocervix or usual type endocervical adenocarcinoma(ECA)[8,11]. However, MUC6 is more widely available than HIK1083, as in our case, we just did MUC6 staining. As GAS is unrelated to high risk HPV(hrHPV) 16[27–30], p16 staining is usually patchy or negative. The lack of estrogen receptors is seen in most GAS, as shown in our case.

The presenting sign of GAS is often mucoid or watery discharge or vaginal bleeding, and widespread involvement and advanced stage are commonly seen when the initial diagnosis is established. Ovarian metastases is not uncommon as well. The biological behavior of GAS is more aggressive compared to usual type ECA; the 5 year survival rate is less than half of that for usual type ECA[31,20]. As patients with GAS usually have an advanced-stage disease and widespread organ involvement, the prognosis of patients with GAS is much worse than that of patients with usual type adenocarcinoma. So in our case, we suggested and finally performed bi-oophorectomy for the patient under her consent. In the meanwhile, as according to the 2018 LACC clinical trial, we improved the surgical procedures of laparoscopic radical hysterectomy. In the surgery, a tape was used for uterus manipulation instead of cup-type uterine trans-cervical manipulator; In addition, colpotomy was done vaginally and the uterus was taken out from the vagina with the cervix wrapped in the vaginal wall cut.

Because of the high risk of malignancy in Peutz-Jeghers syndrome, a more thorough cancer screening has been proposed. Firstly, annual pelvic ultrasound and cervical screening test have been recommended for cancer screening in females older than 18 years old with Peutz-Jeghers syndrome[11,20,1]. Since cytologic 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 Peutz-Jeghers syndrome worth a cervical biopsy even if the patient has no sexual life.

Declarations

- 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 patient. A copy of consent is available for review by the Editor of this journal

- Availability of data and materials

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

- Competing interests

The authors declare that they have no competing interests

- Funding

This research did not receive any specific grants or funding

- Authors' 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

- Acknowledgements

We thank Professor Huijuan Zhang for providing pathology information and guidance of the case.

Abbreviations

PJS: Peutz-Jeghers syndrome

GAS: gastric-type adenocarcinoma

ECA: endocervical adenocarcinoma

HPV: human papilloma virus

UEA: usual-type endocervical adenocarcinoma

MRI: magnetic resonance imaging

CA125: carbohydrate antigen125

CA199: carbohydrate antigen199

SCC: squamous cell carcinoma antigen

CA153: carbohydrate antigen153

CA724: carbohydrate antigen724

CEA: carcino-embryonic antigen

AFP: alpha fetoprotein

HE4: human epididymis protein4

AUC: area under the curve of concentration

SCTAT: sex cord tumour with annular tubules

MDA: minimal deviation adenocarcinoma

WHO: World Health Organization

LEGH: lobular endocervical glandular hyperplasia

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Figures

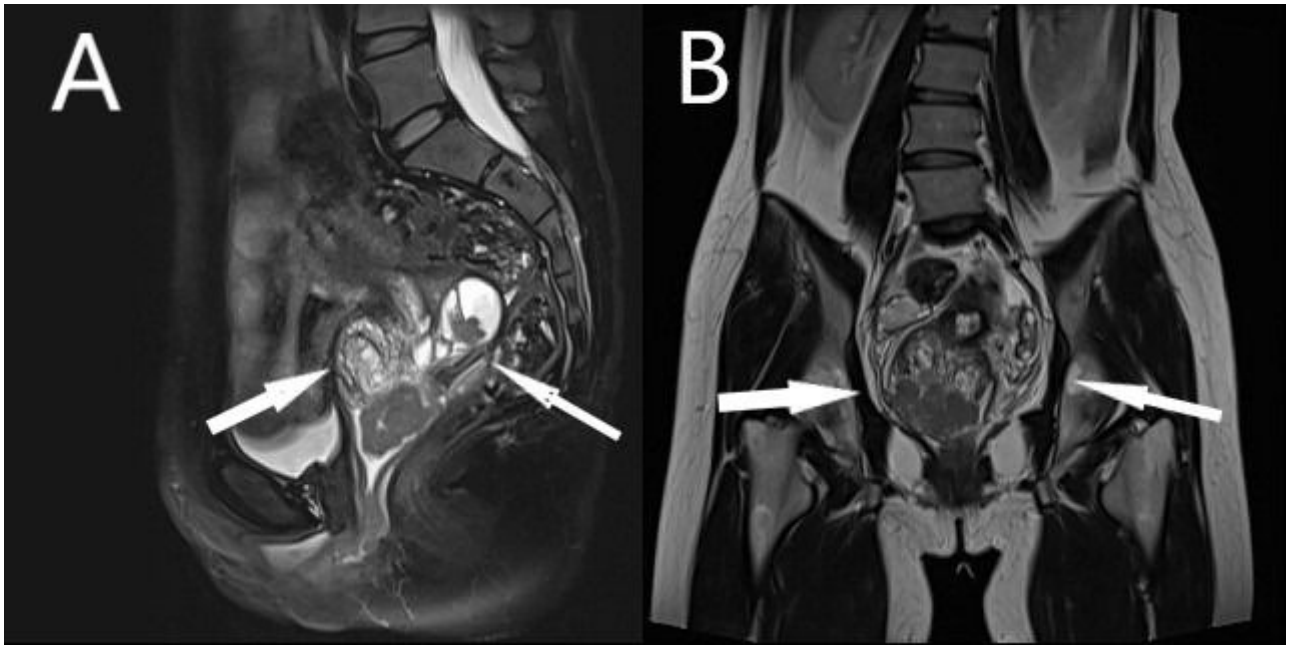

Figure 1

(A,B) Pelvic magnetic resonance image showing a tumor of the cervix with cystic lesions (arrow).

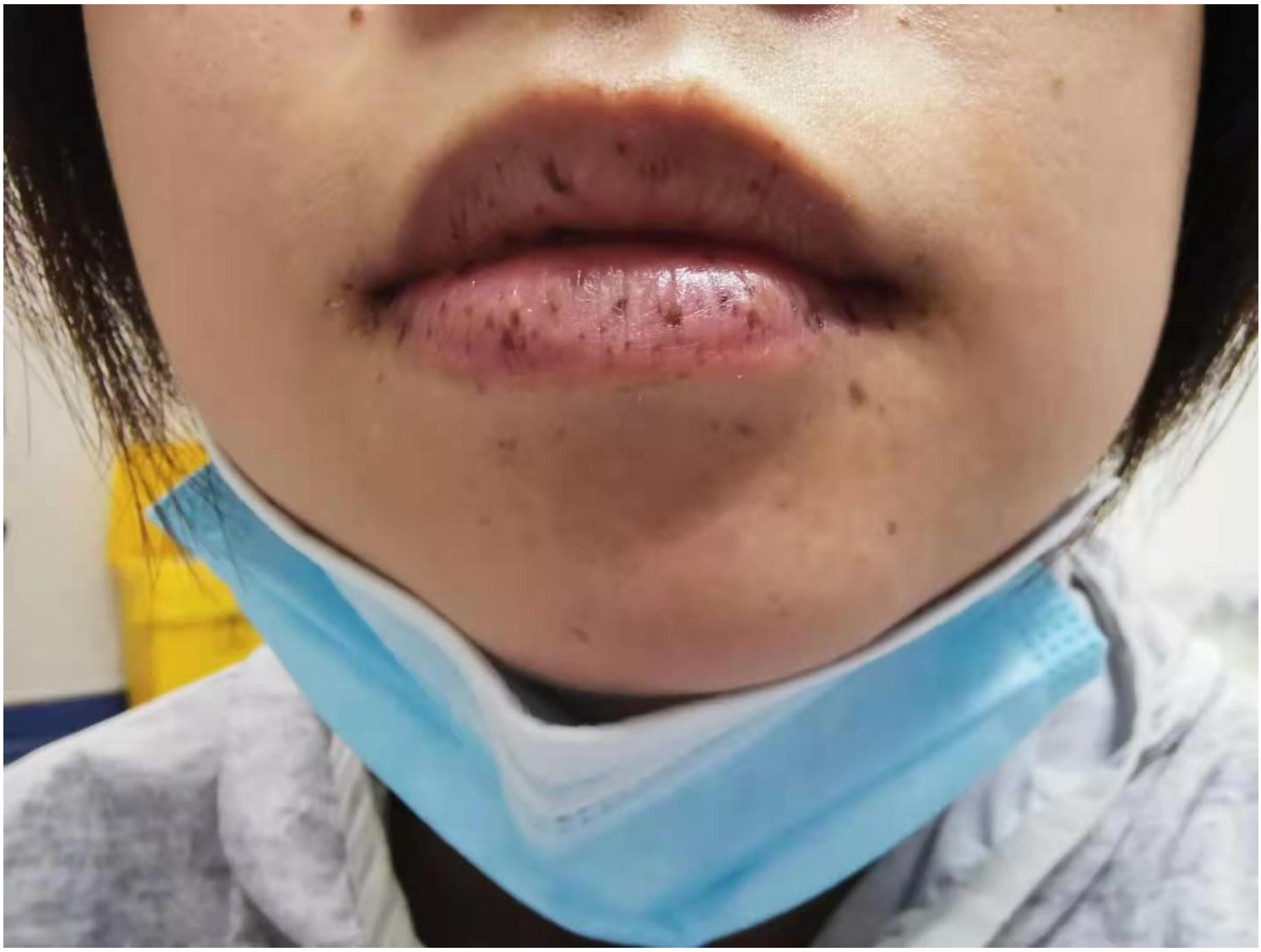

Figure 2

Peutz-Jeghers syndrome patient with pigmentations over the lips, especially the lower lip and nostrils.

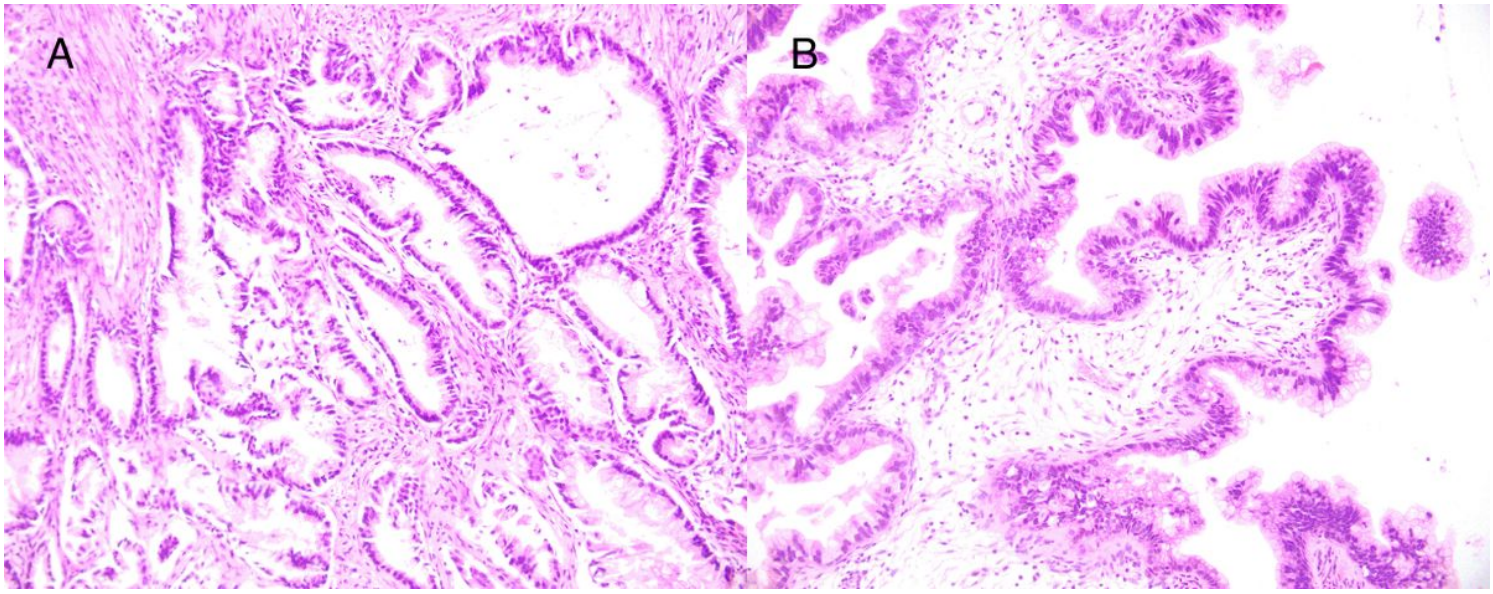

Figure 3

(A,B) Histopathological results of radical surgery.

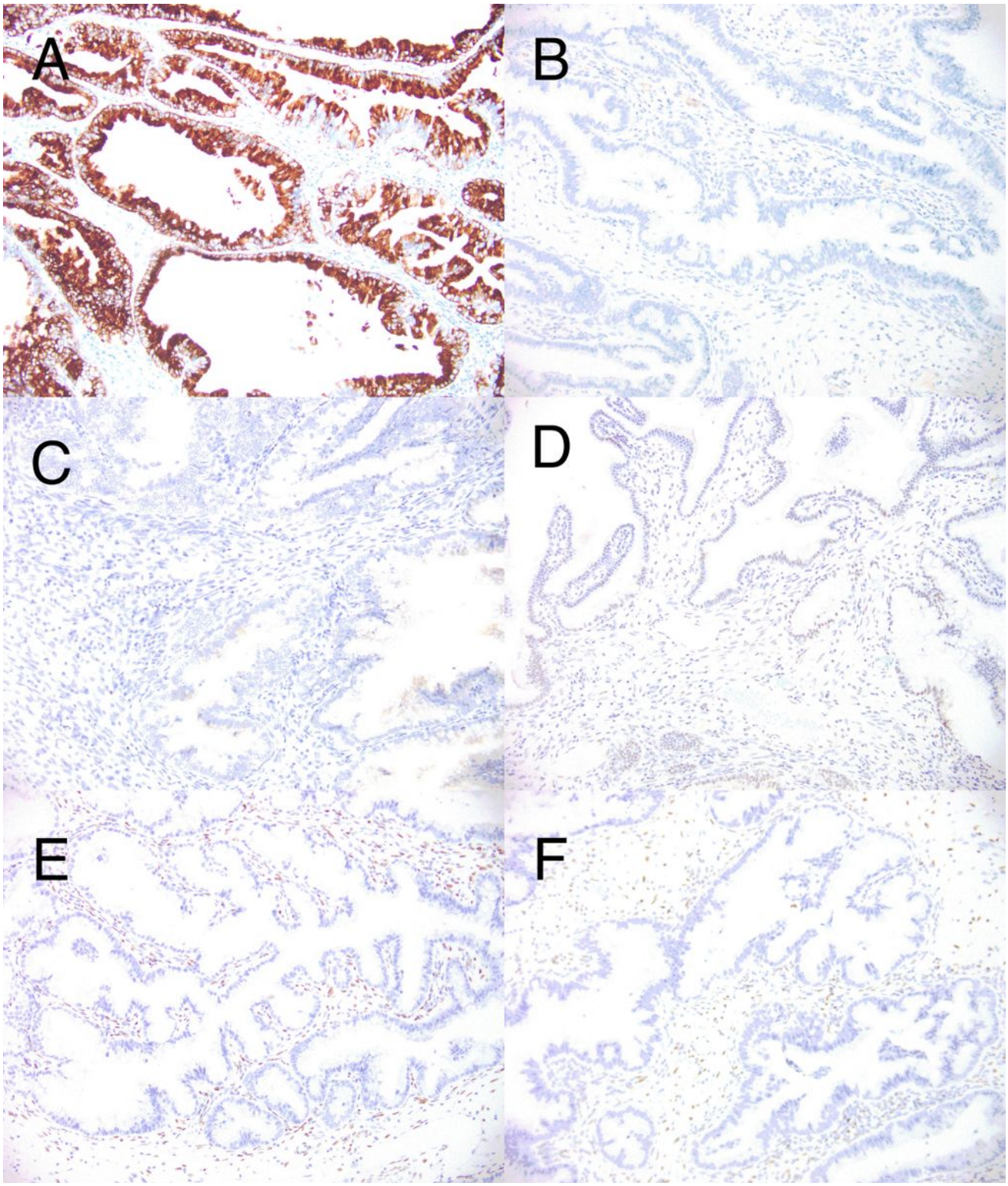

Figure 4

(A) Immunohistochemical staining is positive for MUC6, a marker of pyloric gland mucin; (B) Immunohistochemical staining is negative for MUC2; (C) Immunohistochemical staining is patchy for

P16; (D,E,F) Immunohistochemical staining is negative for P53, ER and PR.