

CASE REPORT

Cervical villoglandular adenocarcinoma: a rare case report and review of the literature

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Abstract

Villoglandular adenocarcinoma (VGA) is a rare variant of cervical adenocarcinoma classified as HPV-associated. We encountered a case of cervical VGA with no evidence of HPV infection reported below. A 50-year-old woman accidentally discovered cervical polyps during gynecological physical examination. After removal, the pathological examination was diagnosed as cervical VGA, and immunohistochemistry showed that p16 was focal positive expression. We reviewed the relevant literature to summarize the clinicopathological features of VGA and the key points of pathological diagnosis and differential diagnosis.

Keywords

Villoglandular adenocarcinoma; Adult; Female; Humans; Cervix; Pathology

1. Introduction

Villoglandular adenocarcinoma (VGA) was first reported by Young and Scully in 1989 and has long existed as a subtype of cervical adenocarcinoma [1]. However, the International Endocervical Adenocarcinoma Criteria and Classification (IECC) and the 5th World Health Organization (WHO) classification of female genital tumours classify cervical adenocarcinomas as human papillomavirus (HPV)-associated and HPV-independent. As a variant, VGA is classified as common endocervical adenocarcinoma which is a subtype of HPV-associated cervical adenocarcinoma [2, 3]. VGA is rare and accounts for less than 1% of endocervical adenocarcinoma. Compared with other common types of cervical adenocarcinoma, VGA has a younger mean age and better prognosis [4].

However, VGAs present diagnostic challenges in pathological diagnosis. Due to the lack of clear histological diagnostic criteria for VGA and the prognostic analysis of large samples in current professional pathology books, and the definition criteria of VGA in different literatures are different, the pathological diagnostic criteria for this subtype are not accurately grasped [5]. As a result, the diagnostic consistency of cervical VGA is not good, the preoperative pathological diagnosis rate is low, and it is easy to cause misdiagnosis and missed diagnosis of cervical VGA [6]. We report a new case of cervical VGA. The clinicopathological features and differential diagnosis with other benign and malignant papillary lesions of the cervix are also discussed.

2. Case report

A 50-year-old female patient came to our outpatient clinic for further treatment because of a cervical polyp found during physical examination. She discovered a cervical polyp during

a routine physical examination and came to the clinic the same day to request its removal. She was in menopause and asymptomatic. She had a history of cesarean section 27 years ago, a history of uterine fibroids for 13 years, and a history of lumbar disc herniation for 9 years. She underwent right radical thyroidectomy and left total thyroidectomy 7 years ago, and the postoperative pathological diagnosis was papillary thyroid carcinoma with two lymph nodes metastases. She takes levothyroxine sodium tablets, 1.5 tablets, once every morning for a long time. A year ago, she underwent cervical polypectomy at another hospital. The biopsy pathological diagnosis described cervical villos glandular tubular adenomatous hyperplasia. At that time, she also performed cervical thin-layer liquid-based cytology and HPV E6/E7 Messenger RNA (mRNA) testing, and the results were not abnormal. Laboratory examination revealed no abnormal findings. Chest computerized tomography (CT) revealed tiny nodules in the lower lobes of both lungs, which were considered proliferative foci. Brain CT scan showed no obvious abnormality. Ultrasonography revealed a leiomyoma of the posterior wall of the uterus, 35 mm × 33 mm in size. The liver, gallbladder, pancreas, spleen, and kidneys were all normal, and there was no obvious abnormality in the bilateral thyroidectomy sites. Her physical examination was unremarkable. A gynecological examination revealed a cervical exophytic lesion, polypoid, about 1 cm in size. The cervical vegetations were then removed.

Gross examination displayed a piece of gray-white tissue measuring 1 cm × 0.8 cm × 0.3 cm. Microscopically, the predominant pathological features are finger-like or branching papillae with a fibrovascular axis (Fig. 1A). The papillae were variable in size and width, lined with tall columnar epithelium, arranged in monolayers or pseudostratified. The nuclei showed mild to moderate atypia, and mitosis was seen

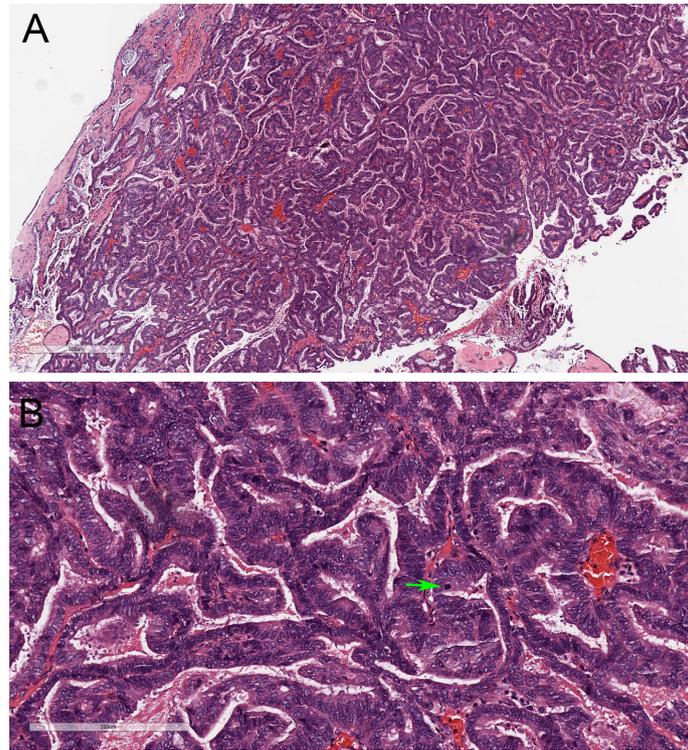


FIGURE 1. Histological examination of villoglandular adenocarcinoma of the cervix. H&E stain. (A) The tumor was exophytic and consisted of irregular glands and branched papillae (scale = 600 μm). (B) The papillary surface is lined with tall columnar epithelium with mild to moderate cellular atypia. Cells are tightly packed and apoptotic bodies are visible (scale = 200 μm).

(Fig. 1B). Immunohistochemical staining showed positive for estrogen receptor (ER), cytokeratin 7 (CK7), vimentin, focally positive for p16 (Fig. 2A–2D), and negative for cytokeratin 20 (CK20), carcinoembryonic antigen (CEA) and p53. The Ki-67 proliferation index was lower in tumor cells (Fig. 2E). The pathological diagnosis was VGA of the cervix.

The patient did not undergo further surgical treatment at our hospital. Two years later, we tried to contact the patient about follow-up treatment. Unfortunately, the patient was lost to follow-up.

3. Discussion

In the previous WHO classification, cervical adenocarcinoma was classified into chorionic adenocarcinoma, endometrioid carcinoma, and serous carcinoma according to morphological classification, which was poorly reproducible and had no biological basis. Therefore, the 2020 WHO classification divides cervical adenocarcinoma into HPV-associated and HPV-independent. Characteristic apical mitotic and apoptotic bodies are frequently present in HPV-associated adenocarcinomas. As HPV-associated adenocarcinomas almost always show diffuse bulk immunoreactivity to p16. Therefore, p16 immunohistochemistry may be useful in determining whether tumors are HPV-associated or HPV-independent. Possibly secondary to deletion or methylation, total or local loss of p16 occasionally occurs during tumor progression [2], as shown in our case.

VGAs have a distinct exophytic, villous-papillary growth pattern. As a rare subtype of cervical adenocarcinoma, its

prognosis is excellent and corresponds to type A of the Silva system [7]. The consistency of pathological diagnosis of cervical VGA is relatively low. In a study of the reproducibility of the diagnosis of cervical adenocarcinoma, only 3 of 15 cervical VGAs were consistent with the original diagnosis at reassessment [8]. Due to the low diagnostic accuracy of cervical biopsy, the diagnosis of VGA mainly relies on final histopathology [9]. We summarize the histological features of cervical VGA including the following. Macroscopically, VGAs usually appear as exophytic, well-circumscribed, friable, and variable-sized masses. It is characterized by a luminal mitotic map and relatively mucin-depleted cells. It has characteristic exophytic villous papillary structures with varying papillary widths and a fibrovascular stroma along the papillary axis. The papillary surface is lined with tall columnar endocervical epithelial cells, which may contain a small amount of mucus or no mucus, and the nuclei are arranged in monolayer or pseudostratified. VGA usually presents only as a superficial invasion. If deeper invasion occurs, the tissue structures appear as glands rather than papillae. Tumors may have little or no stromal response, but usually have at least localized desmoplastic stroma [10].

Histopathological diagnosis of VGA is difficult because approximately 30% of VGAs occur in other types of invasive cancers [11]. Immunohistochemical examination may be helpful for the pathological diagnosis of VGA. Ki-67, p53, p16, CEA, Vim, and ER were all positively expressed to varying degrees in VGA, but progesterone receptor (PR) was hardly detected [11, 12]. Diffuse blocking-type immunoreactivity to p16

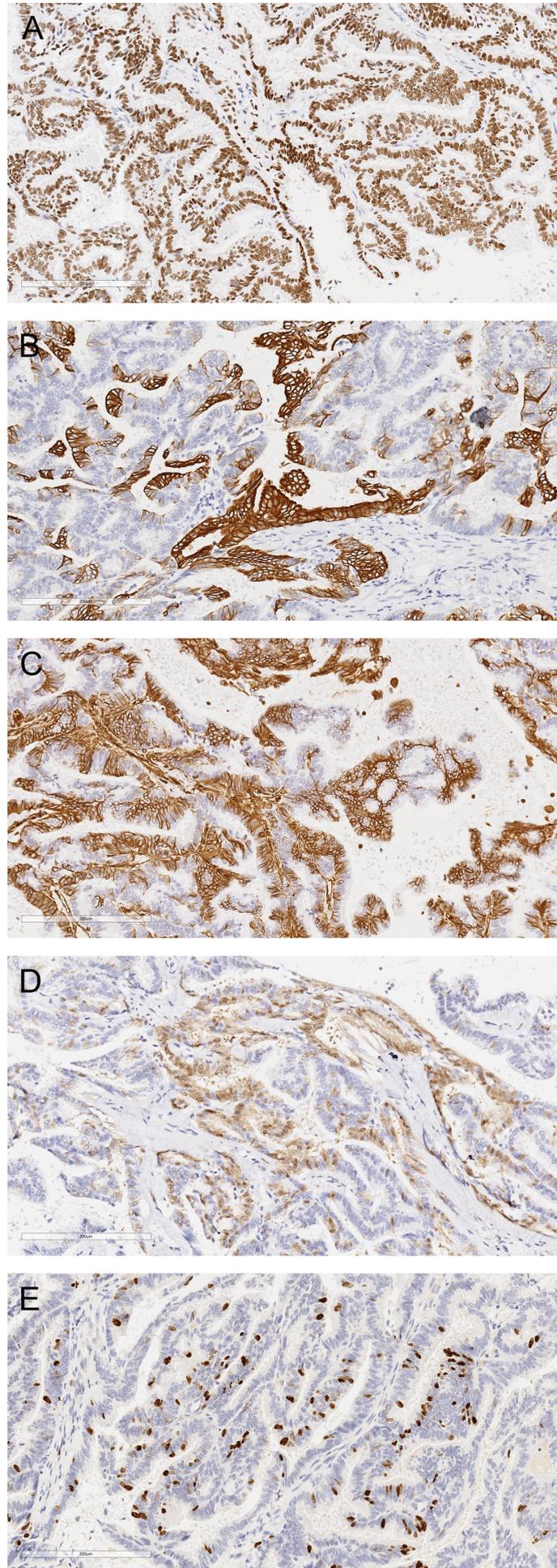


FIGURE 2. Immunohistochemical staining (scale = 200 μm). (A) ER positive. (B) CK7 positive. (C) vimentin positive. (D) focally positive for p16. (E) a lower proliferation index of Ki-67.

is almost always present in HPV-associated adenocarcinomas [13]. However, our case was peculiar in that histologically, it exhibited the histological morphology of a VGA, whereas immunohistochemically, p16 was focal positive expression.

Our patient has a history of papillary thyroid carcinoma, which needs to be differentiated because both form papillary structures. We reviewed the pathological section of this patient's papillary thyroid carcinoma and found that the thyroid carcinoma had a glialoid component, and the cells were cuboidal rather than tall columnar and lacked ciliated structures. In addition, papillary thyroid carcinoma expresses thyroglobulin (TG) and transcription termination factor 1 (TTF-1), while cervical VGA expresses ER, p16 and Vimentin.

In clinicopathological diagnosis, VGA needs to be differentiated from other benign or malignant tumors of the cervix with villous tubular or papillary structures: (1) Serous carcinoma of the cervix is not included in the 2020 WHO Classification. Most tumors previously diagnosed as such represent common type HPV-associated cervical adenocarcinomas with papillary architecture and high-grade nuclear features or direct involvement by a drop metastasis of a tubo-ovarian or endometrial serous carcinoma [13]. Cervical serous carcinomas with papillary architecture and high-grade nuclear features and primary HPV-associated cervical adenocarcinomas presenting as serous carcinomas almost always show wild-type p53 staining. Metastases from tubo-ovarian or endometrial serous carcinomas are true "high-grade" serous carcinomas that are almost always immunoreactive with mutant p53. WT1 transcription factor (WT1) helps to rule out metastases derived from tubo-ovarian cancer. (2) Endometrioid carcinoma is an extremely rare type of primary cervical HPV-independent adenocarcinoma. These tumors are thought to arise primarily from cervical endometriosis. Diagnosis should only be made when a primary tumor in the uterus is excluded. (3) Metastasis of colorectal villous adenocarcinoma to the cervix is rare, and the main distinguishing point is clinical history. Metastatic carcinomas have a large atypia and are often accompanied by necrosis. The immunophenotype of colorectal villous adenocarcinoma expresses CK20, Villin, and caudal type homeobox 2 (CDX2), but not CK7. (4) Mullerian papilloma is a rare benign papillary tumor of childhood consisting of slender fibrous papillae covered by a single layer of cuboidal or columnar epithelium, with mild cell morphology and no atypia or mitoses. (5) Papillary adenofibroma is a benign tumor that rarely occurs in the cervix. The papillary epithelium is benign, without atypia, and generally consists of tightly packed cuboidal or columnar glandular epithelium, and the papillary stroma is mainly composed of spindle-shaped or astrocytic fibroblasts. In some cases, mitotic figures and occasional mat-like structures can be seen. (6) Minimal deviation adenocarcinoma is a rare well-differentiated adenocarcinoma with minimal or only mild cellular atypia. The glands are disorganized and papillary structures are relatively rare.

Villoglandular variants of common-type endocervical adenocarcinoma are rarely associated with lymphovascular invasion and lymph node metastasis and usually lack or show only superficial stromal invasion [13]. With only superficial invasion, VGA typically have an excellent prognosis; however, when invasion is deeper and resembles that of stan-

dard common-type endocervical adenocarcinoma, clinical outcomes are similar to those of other common-type endocervical adenocarcinomas. Due to the lack of pathological examination results of surgical specimens in our case, the degree of invasion cannot be evaluated, and the combination of other types of cervical adenocarcinoma cannot be ruled out.

Recently, an independent cohort study found that HPV-associated endocervical adenocarcinomas presented at a lower age, smaller tumor sizes, less margin positivity, less Silva pattern C, and lower International Federation of Gynecology and Obstetrics (FIGO) stages [14]. HPV-associated cervical adenocarcinomas are less frequently associated with lymphovascular invasion and lymph node metastasis [15]. HPV-associated endocervical adenocarcinoma had superior survival compared with HPV-independent endocervical adenocarcinoma. Regardless of HPV status, factors associated with poorer prognosis were FIGO stage, positive resection margins, and lymphovascular invasion [14, 15].

AUTHOR CONTRIBUTIONS

XBL wrote the draft manuscript. CLH made the pathological examination. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Young RH, Scully RE. Villoglandular papillary adenocarcinoma of the uterine cervix. A clinicopathologic analysis of 13 cases. *Cancer*. 1989; 63: 1773–1779.
- [2] McCluggage WG, Singh N, Gilks CB. Key changes to the world health organization (WHO) classification of female genital tumours introduced in the 5th edition (2020) histopathology. 2022; 80: 762–778.
- [3] Stolnicu S, Barsan I, Hoang L, Patel P, Terinte C, Pesci A, *et al.* International endocervical adenocarcinoma criteria and classification (IECC). *American Journal of Surgical Pathology*. 2018; 42: 214–226.
- [4] Turashvili G, Park KJ. Cervical glandular neoplasia. *Surgical Pathology Clinics*. 2019; 12: 281–313.
- [5] Heatley MK. Villoglandular adenocarcinoma of the uterine cervix? A systematic review of the literature. *Histopathology*. 2007; 51: 268–269.
- [6] Korach J, Machtinger R, Perri T, Vicus D, Segal J, Fridman E, *et al.* Villoglandular papillary adenocarcinoma of the uterine cervix: a

- diagnostic challenge. *Acta Obstetrica et Gynecologica Scandinavica*. 2009; 88: 355–358.
- [7] Zhang Y, Wang Y, Liu Y, Yang J, Liu C. A retrospective study and literature review of cervical villoglandular adenocarcinoma: a candidate paradigm of silva system pattern A. *Applied Immunohistochemistry & Molecular Morphology*. 2021; 29: 467–472.
- [8] Alfsen GC, Reed W, Abeler VM. Reproducibility of classification in non-squamous cell carcinomas of the uterine cervix. *Gynecologic Oncology*. 2003; 90: 282–289.
- [9] Zhao L, Xu T, Cui M, Fu Z. A retrospective review of 11 cases of villoglandular papillary adenocarcinoma of the uterine cervix and a review of the literature. *Oncology Letters*. 2016; 11: 2164–2168.
- [10] Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. *Histopathology*. 2002; 41: 185–207.
- [11] Shen H, Huang Z, Zhang S, Zhang Y, An J, Luo J, *et al*. The clinicopathologic and immunohistochemical features of villoglandular adenocarcinoma of uterine cervix. *Indian Journal of Pathology and Microbiology*. 2018; 61: 549.
- [12] Guo P, Liu P, Yang J, Ren T, Xiang Y. Villoglandular adenocarcinoma of cervix: Pathologic features, clinical management, and outcome. *Cancer Management and Research*. 2018; 10: 3955–3961.
- [13] McCluggage WG. Progress in the pathological arena of gynecological cancers. *International Journal of Gynecology & Obstetrics*. 2021; 155: 107–114.
- [14] Ren H, Almadani N, Pors J, Leung S, Ho J, Chow C, *et al*. International endocervical adenocarcinoma criteria and classification (IECC): an independent cohort with clinical and molecular findings. *International Journal of Gynecological Pathology*. 2021; 40: 533–540.
- [15] Stolnicu S, Hoang L, Soslow RA. Recent advances in invasive adenocarcinoma of the cervix. *Virchows Archiv*. 2019; 475: 537–549.

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