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Villoglandular Papillary Adenocarcinoma of the Uterine Cervix: Four Clinical Cases Report and Literature Review

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Abstract

Background: Villoglandular papillary adenocarcinoma(VGA) of the uterine cervix is a rare subset of cervical cancer. It was reported to have a better prognosis than some other pathological types and generally occurred in young women at reproductive age. According to the excellent prognosis, it has been suggested that a less radical surgical procedure is feasible.

Method: Four cases were retrospectively reported. Information on their clinical characteristics, management, pathological results, and outcomes was reviewed.

Results: Except for one lost follow-up, the follow-up period for the remaining three has lasted over 10 years. Between the two patients who accepted ovary preservation, one found disease recurrence and was treated by biological immunotherapy and received good control.

Conclusion: For patients in the early stages, radical hysterectomy or ovarian preservation should be considerable choices, especially for young patients with clear indications. Once the recurrence of the disease occurs, biological immunotherapy should be considered and may receive satisfactory control effects.

Keywords: Villoglandular Papillary Adenocarcinoma (VGA); Cervical Cancer; Ovary Preservation; Recurrence; Bevacizumab; Tislelizumab

Case Report

Case 1: A 49-year-old female, gravida 2, para 2, presented to our hospital with a chief complaint of postcoital bleeding for about half a year. During the two months before this visit, watery vaginal discharge was noticed. The patient had no history of using oral contraceptives. Thinprep cytologic test (TCT) and human papillomavirus (HPV) details were unavailable. The pathological result from the local hospital reported endometrioid adenocarcinoma. However, the result of group consultation from our hospital showed atypical hyperplasia of the endometrium with focal carcinoma. Gynecological examination revealed a 3-cm exophytic, hemorrhagic, friable lesion on the anterior lip of the cervix. Vagino-recto-abdominal examination revealed no evidence of paracervical or parametrial involvement. Due to the inconsistent results, we arranged segmental curettage and multipoint biopsy of the cervix. The pathological result showed villoglandular papillary adenocarcinoma(VGA). The rest of the examinations were normal. The clinical stage was lb1, according to FIGO. Laparoscopic radical hysterectomy with bilateral salpin-go-oophrectomy and bilateral pelvic lymphadenectomy was performed without delay. The final pathological diagnosis was moderately to well-differentiated VGA. Both the depth and width of invasion were 1.2cm under the microscope. Ki-67 index was (+, 75%) and P16 was (+). Lymph nodes, vaginal stump, and bilateral parametrial invasion were not observed. It is more than 35 months post-operation, and the latest follow-up report shows no signs of tumor recurrence. The patient accepted preventive TC chemotherapy after the surgery.

Case 2:A 37-year-old female, gravida 2, para 1, who preferred our institution, complained that she was diagnosed with cervical cancer through physical examination after more than 5 months of postcoital bleeding in another hospital. HPV DNA was positive. She was told to have a cervical neoplasm of about 2.5*2.0 cm and accepted hysteroscopy and segmental curettage. The pathological report said papillary adenocarcinoma of the cervix. Immunohistochemical result of Ki-67 index was (+, 70%), P16 was (+) and Hc2 was (+). The patient refused to accept surgery there and required further examination. The pelvic examination had no apparent abnormal findings. PET-CT pointed out an abnormal active metabolism area located in the uterine cervix. The diagnosis was lb1 according to FIGO. We arranged a laparoscopic radical hysterectomy with bilateral salpingectomy and bilateral pelvic lymphadenectomy(LRHBS). The final pathological diagnosis was VGA of the cervix. The invasion of the cervical wall was within 1/3. Besides, part of the cervical tissue was found to have intraepithelial neoplasia. Immunohistochemical result of Ki-67 index was (+, 50%) and P16 was (+). Bilateral pelvic lymph nodes were not involved. The bilateral parametria and vaginal margin were clean. This is the eleventh year of her uneventful follow-up.

Case 3: A 36-year-old female, Gravida 3 Para 1, came to our center with a chief complaint of postcoital bleeding for 5 months. She had been taking OC for 3 years but stopped for a while. The TCT result was LSIL, and the HPV-18 was positive. Colposcopy biopsy result showed moderately differentiated adenocarcinoma of the cervix and with a partially CIN-III. SCC was within normal limits. There was no apparent abnormal finding according to the pelvic examination. Cervical conization was performed, and the pathological result showed well-differentiated VGA of the cervix (8mm in width and 4mm in depth invasion) with CIN-II-II. The diagnosis was Ib1 VGA of the cervix according to FIGO. Four weeks later, this patient accepted laparoscopic radical hysterectomy with bilateral salpingectomy, bilateral pelvic lymphadenectomy, and bilateral ovarian suspension. The final pathological diagnosis report was a well-differentiated VGA of the cervix. The depth of invasion was within 1/2 cervical wall, and the lower uterine segment was involved. Part of the tissue was found to be CIN-II-II. With glandular involvement. Immunohistochemical result of Ki-67 index was (+, 30%) and P16 was (+). Bilateral pelvic lymph nodes were not involved. Parametria and the vaginal margin were clear of disease. (Fig.1) In the sixth-month follow-up, an HPV test of the vaginal vault showed type 18 positive. After 9 months of reexamination, the result was still the same. We arranged a colposcopy and biopsy 3 days later. The white vinegar epithelium was apparent, and the biopsy result showed VIN-II. Then she accepted an excision of the local lesion; no severe lesion was reported according to the pathology report. Then, she gets through a long period of uneventful follow-up. Until January 2023, when she gets into her tenth year of follow-up, the CT scan and ultrasound examination both find the tumor recurrence lesions. The laparoscopy exploration and multi-biopsy surgery were arranged soon. Pathological reports showed bilateral ovarian metastasis and infiltration of moderately differentiated villoglandular papillary adenocarcinoma. The immunohistochemical result of the P16 index was positive diffusely, and Ki-67 was (+, 90%). PD-L1 detection was found positive with the positive control and negative with the negative control test. After that, the patient received chemotherapy of TC for 8 cycles and added bevacizumab from the third cycle of TC chemotherapy. After that, she experienced 5 cycles of bevacizumab monotherapy. From the twelfth cycle, the treatment plan changed to a combination of Bevacizumab plus Tislelizumab. Now, she has finished her 28 cycles of Bevacizumab treatment plus 17 cycles of Tislelizumab. The PET-CT scan last month showed no evidence of recurrence. Severe treatment complications have not been observed until now, and the patient feels generally well.

Case 4: A 27-year-old female, Gravida 3 Para 1, visited our hospital with a chief complaint of the discovery of cervical neoplasm found during a physical examination 5 days ago. According to the pelvic examination at the clinic, there was a neoplasm about 1.0*1.5cm on the Posterior labium of the cervix with contact bleeding. Then the patient accepted the excision of the cervical neoplasm. Pathological reports both showed cervical squamous cell carcinoma and VGA. However, the patient lost follow-up.

	Case 1	Case 2	Case 3	Case 4
Age(years)	49	37	36	27
Symptom	post-coital spotting	irregular vaginal bleeding	post-coital bleeding	cervical neoplasm
OC usage	Ν	Ν	more than 1 year	Ν
HPV infection	-	high risks HPV DNA+	HPV-18	-
Lesion size	3cm, exogenous	2.5*2.0cm neoplasm	-	1.5*1.0cm neoplasm
Type of biopsy	cervical biopsy+ECC	cervical neoplasm excision	colposcopic biopsy	neoplasm excision
FIGO stage	IB1	IB1	IB1	unclear
Surgery	LRHBSO+LN	LRH+LN	LRH+LN	-
Ovarian preservation	No	Yes	Yes	unknown
Pathological result	Moderate-to-well differentiated VGA	Well-differentiated VGA+CIN	Well-differentiated VGA+CIN-∥~Ⅲ	VGA+SCC
LN metastasis	-	-	-	unknown
Additional treatment	TC chemotherapy	none	none	-
Follow-up (years)	11	11	11/recurrence	lost

Fable 1: Clinica	l Pathologic	Findings of	f the Four Cases
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Figure 1: Histologic findings of case 3. (A) H&E stain,◊10. CIN-III lesion. (B) P16 stain,◊4. (C) H&E stain,◊4. (D) VIMT stain,◊10. Pictures B, C, and D present well-formed papillary structures and show HPV infection relevant.
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Discussion

Adenocarcinoma accounts for about 20% -25% of invasive carcinomas of the uterine cervix in recent years[1,2,3], rising from approximately 5% before 1970[4,5]. Villoglandular papillary adenocarcinoma(VGA) is a rare subtype of adenocarcinoma of the uterine cervix, which accounts for about 4.8~8.1% of all cervical adenocarcinoma[6,7] and is reported to have a better prognosis than other subtypes. In 1989, Young and Scully described 13 cases in their report[8]. They pointed out that cone excision was available for those patients who proved no more than 3mm depth of invasion, a clear margin, and no evidence of vascular invasion, and the patient should be followed with great care after the operation. We consulted some of the literature, and some suggested that rigorously defined well-differentiated VGA could receive a fine prognosis through cervical conization [6,7,9]. However, coexistence with other pathologically invasive types or metastasis disease in the early stage occurred in a few cases, which may affect the diagnosis and treatment. James S Hoffman et al. make a summary from 5 studies that in 30% of cases, VGA conjugated with other forms of invasive cervical cancer[9-13]. Aruna and Kuniko found lymph node metastasis in their studies[14,15]. Because of these circumstances, the argument still focuses on the diagnosis and different types of treatment. In this report, we described 4 new cases of VGA, including the treatment and follow-up details.

Among our 4 cases, three of them underwent HPV tests and showed positive results. Only one patient accepted conization and made a clear diagnosis before the secondary treatment. The other three patients only accepted a biopsy at the beginning, and the diagnosis showed deviation from the final pathological results. We have known that the detection accuracy rate of adenocarcinoma is known to be significantly lower than that of squamous cell carcinoma. Krane JF pointed out that adenocarcinoma cells, potentially mistaken for intimal cells in the lower uterus or cervical cells with tubo-endometrioid metaplasia, were the reason for the lower detection rate of glandular cell abnormalities[16]. In Sriomboon Spointed's paper, they examined 75 patients with AIS diagnosed after cone, but glandular abnormalities were only found in 37.3% of them[17]. Delia B. Dalbert concluded in their paper that HCC (hidden cervical cancer) had a worse evaluation and poor outcome significantly greater than in patients with EEC (ectocervical or exo-endocervical cancer), because the lesion originated high up in the cervical canal evolves hidden or inaccessible to diagnostic methods, and the use of virological tests in the screening would allow to detect HCC in early stages[18]. What's more, adenocarcinoma in situ often coexists with other pathological types of invasive cancer. According to HUGH M, etc., mixtures of adenocarcinoma and squamous cell carcinoma occur in one-third of the patients, and squamous intraepithelial neoplasia occurs in one-tenth of the patients[19]. In this situation, making a completely clear diagnosis based on biopsy is significantly difficult. Refer this subtype, the good aspect is that this subtype is proven to be HPVA cervical cancer, which would receive a better prognosis than the NHPVA type, while the pitfall is precisely identifying the tumor nature before the second treatment[20-22]. Remi Hasegawa pointed out in their case report that asymptomatic VGA may show the same macroscopic findings as an asymptomatic cervical polyp and with negative cytology, but coexist with CIN[10]. According to the meta-analysis from Anna K. Dietl etc., it's a challenge to make a precise histological diagnosis of VGA, and they suggest the pretreatment should better be based on conization with wide tumor-free margins rather than simple punch biopsy, as for the exogenous lesion types, the invasion and depth inside cervix could not be exactly involved[23]. In the study of cancer of the cervix uteri: 2021 update, they suggest that the diagnosis of stages IA1 and IA2 is made on microscopic examination of a cone biopsy specimen, for it includes the entire lesion[24]. In case of a visible lesion, a punch biopsy may be generally sufficient for diagnosis, or else, a loop biopsy or cone may be required.

Get back to our four cases, the 37-year-old patient and the 27-year-old patient both showed a typical cervical neoplasm. The biopsy results only referred to adenocarcinoma without subtype details for the previous one, while the other found VGA coexisting with squamous cell carcinoma. Both the 36-year-old patient and the 49-year-old patient had found an almost normal appearance of the cervix, while clear results came up from the cone biopsy. Except for the 27-year-old patient who was lost to follow-up, the rest three were accepted LRHBSO and LN or LRHBS and LN afterward. All of them found VPA through the patho-

logical examination, and two of them found CIN at the same time. Concluding the viewpoint from previous pieces of literature, we find that VPA could coexist with other types of invasive cervical cancer or precancerous lesions, and it should be a good reason to perform a cone at the start to make clear[7].

Under the premise of a precise pathological result, the treatment would be arranged more properly, we could fix the treatment varying with each individual. For those patients with early stages, treatment plans are fixed according to the clinical stage, fertility requirements, age, risk factors, etc. Reviewing the literature, we have checked out from PUBMED, we find that 18 cases accepted only cold knife cone excision, whose clinical stages are between IA1 and IB2[6,8,12,25-31]. Only one of them, with clinical stage IB2, had a recurrence and died of the disease [15]. The initial invasion of this patient was 24mm*2.4mm with a clear margin. Nevertheless, only 3 months later, the recurrence was moted by MRI, and died of rapid tumor progression and pelvic completion then. There were another 6 cases of stage IB1 accepted radical trachelectomy, and all of them received a good prognosis[28,32,33]. If the conservative surgical plan could achieve a certain effect, it would have great significance for the pregnancy and those who have reproductive function preservation requirements. Yet, the final decision has not been made regarding whether the upper clinical stage limit of fertility preservation surgery for VGA patients is IB1. Even if the malignancy degree is low, we still need to be cautious about metastasis. From the papers of Aruna and Kuniko, they pointed out in their case report that even in the early stage, lymph node metastasis could be possible [14,15]. For those young patients of reproductive age, especially those who have fertility preservation requests, this is an independent risk factor affecting prognosis. To lower the risk, sentinel lymph node mapping is a reliable method to detect lymph node metastases in early-stage cervical cancer, and it could be an acceptable treatment strategy for selected patients with small-volume stage I cervical cancer[34]. In the 2023 NCCN guideline of cervical cancer, recommendations for SLN mapping were also described in detail.

Besides the lymph node metastasis, ovarian metastasis is another important aspect affecting the treatment plan for adenocarcinoma patients. As the patients are relatively young, not only for those patients who need fertility preservation but also for those who are far from stepping into the peri-menopausal period, ovarian function plays an important role in normal endocrine function. For decades, the indication of ovarian preservation has still been inconsistent[35,36] because the metastasis rates rise with the clinical stages. Even so, according to the latest papers, the ovarian preservation rate has kept growing during the last 10 years[37], and the OS and PFS are of no significant differences for those patients with early stages[38]. A meta-analysis reported that for those clinical stages ranging from IA~IIB, there is no significance for 5-year OS and 5-year DSS between the two groups regarding whether to reserve the ovary in the surgery[39]. According to Sheng J and Wang SS, they pointed out that those who accepted ovarian preservation of T1N0M0 seem to get a better DSS and OS, but for those whose stages exceed IIB, the ovary should not be reserved, for the metastasis rate is significantly higher[39,40].

Among the three patients we have had regular follow-up information, all of them are of IB1 FIGO stage before surgery. Two of them accepted LRHBS with bilateral pelvic lymphadenectomy, under the premise of no fertility requirements. According to the pathological reports after surgery, one of them is well-differentiated, while the other two are moderately to well-differentiated with squamous intraepithelial neoplasia. The invasion of depth didn't exceed 1/3 or 1/2 cervical wall, respectively. Both of them chose to preserve bilateral ovaries. One had received a more than ten-year follow-up without recurrence, while the other found recurrence in her eleventh year of follow-up and accepted targeted therapy with immunotherapy.

The targeted therapy for recurrent or metastatic cervical cancer treatment was started only in recent years, and PD-1/PD-L1 inhibitors were recommended for the treatment of recurrent or metastatic cervical cancer according to Version 1 of the 2025 NC-CN Cervical Cancer Clinical Practice Guidelines. In China, Tislelizumab is a native PD-1 and has been used in the past two or three years to treat several solid tumors[41-44], including locally advanced cervical cancer and recurrent/metastatic cervical cancer cases. It is an anti-programmed cell death 1 monoclonal antibody, which minimizes binding to Fcy receptors[45]. Xiaojing Zheng, et al. reported that it can demonstrate a statistically significant survival benefit with a tolerable safety profile in patients with recurrent/metastatic cervical cancer[46].

Due to the satisfactory antitumor effects for the solid tumors and acceptable safety profile, Tislelizumab has received approvals in China.

Reviewing the 271 patients from the relevant literature[23], 20% of the patients were treated by conservative treatment and 80% by invasive management. Both the recurrences of disease were 4%. With this favorable prognosis, conservative surgery may be suitable for those in the early stages.

Summary

In conclusion, it seems we could perform a conization and sentinel lymph node mapping for patients with pure VGA of stage IA1 and IB1, without other moderate to high-risk factors. Trachelectomy may be a considerable choice for those young patients who are no more than IB1 with any factors that are not properly fit for cone while having a strong fertility reservation request, and the invasion of the local lesion should not be more than 2cm. Ovary preservation may be a better choice for young patients in the early stages. A hysterectomy should be considered according to the clinical examinations when the stage exceeds IB1. However, we still need to pay close attention to the high-risk factors, such as the lesions close to the margins, lymph node metastasis, etc. When the disease recurs or metastasizes, targeted therapy with immunotherapy should be recommended. We still considered that further statistics were needed to draw a more convincing conclusion.

Author Contributions

Conceptualization: Nan Wu, Hui Yu. Data curation: Hui Yu, Guiqing Gao. Data curation: Hui Yu, Hua Jin, Nan Wu, Guiqing Gao. Investigation: Hui Yu. Methodology: Nan Wu, Hui Yu. Resources: Yujin Zhang, Shuhe Wang, Limei Wang, Supervision: Nan Wu, Guiqing Gao. Validation: Hui Yu, Nan Wu, Guiqing Gao. Writing-original draft: Hui Yu. Visualization: Hui Yu, Hua Jin. Writing-review & editing: Hui Yu

Conflict of interest

The authors declare that there are no conflicts of interest

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