

A Retrospective Study and Literature Review of Cervical Villoglandular Adenocarcinoma: A Candidate Paradigm of Silva System Pattern A

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Abstract: The aim was to investigate the clinicopathologic characters of cervical villoglandular adenocarcinoma (VGA), the authors retrospectively reviewed 4 cases of VGA, including clinical characteristics, pathology, managements, together with outcome information. The median age of the patients was 42 (range: 37 to 58), with 3 of them presenting with stage IB disease and 1 presenting with IVB. Human papillomavirus infection was tested in 3 of the patients, with all positive with high-risk type. Three of the patients underwent a radical hysterectomy with bilateral salpingo-oophorectomy plus bilateral pelvic lymphadenectomy, and 2 of them underwent subsequent chemotherapy. One patient received a bilateral salpingo-oophorectomy plus pelvic and periaortic lymphadenectomy and postoperative radiochemotherapy. Lymph node metastasis was detected in 1 patient. The follow-up time ranged from 56 to 120 months (median: 70 mo). Except for 1 person who experienced recurrence, all patients are alive at present and no recurrence occurred. In conclusion, VGA is a rare subtype of adenocarcinoma of the uterine cervix with distinct exophytic, villous-papillary growth pattern and extremely excellent prognosis, which corresponds with pattern A in Silva system, while its underlying mechanism and genetic background is still far from well known.

Key Words: cervical villoglandular adenocarcinoma, clinicopathology, genetic background, Silva system

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Cervical adenocarcinoma comprises 10% to 18% of all cervical cancers, and it appears to be increasing in absolute number of cases as well as in relative percentage

of invasive cervical tumors diagnosed. Adenocarcinomas are more likely to be locally advanced when diagnosed,^{1,2} less responsive to radiation therapy, and hence more likely to result in death.³ The different molecular events underlying may contribute to their histologic features, enhance tumor heterogeneity, and ultimately sustain metastatic dissemination.

As a rare subtype of cervical adenocarcinoma, cervical villoglandular adenocarcinoma (VGA) was first reported in 1989 by Young and Scully.⁴ They suggested that VGA was distinct from other subtypes of cervical adenocarcinoma for its relatively favorable prognosis and earlier onset. It is defined as a variant of endocervical adenocarcinoma which shows a distinct exophytic, villous-papillary growth, and it is emphasized that the invasion of VGA should be typically superficial but it might exhibit deep stromal invasion occasionally.⁵ Given that superficially invasive VGA is rarely associated with lymph node metastasis (LNM), conservative treatment has been suggested. However, more aggressive cases including LNM, recurrence and even mortality have also been reported.^{6–10} Therefore, treatment decisions should be made based on complete excisions, including conization, rather than biopsy.⁵

In this paper we reported a series of 4 cases of VGA at our institution with descriptions of their clinicopathologic features. The age of the patients ranged from 37 to 58, and none of them showed evidence of tumor recurrence after treatment.

MATERIAL AND METHODS

Case Review

Clinical History and Sequence of Events

Case 1: a 44-year-old women (gravida 5, para 3) was referred to our hospital for evaluation on March 25, 2010 after an abnormal cervical biopsy in other medical center, which showed moderated-differentiated villoglandular papillary adenocarcinoma. She was subsequently dealt with a radical hysterectomy with bilateral salpingo-oophorectomy (BSO) and bilateral pelvic lymphadenectomy (PL) and was finally proved to be Federation International of Gynecology and Obstetrics (FIGO) IB1 with tumor superficially confining within 0.5 mm in depth of the cervical wall. An adjuvant chemotherapy of 2 months was applied and there was no recurrence after 120-month follow-up.

Case 2: a 37-year-old female (gravida 3, para 1) presented to our center on September 9, 2013, because of

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increasing amount of yellow-colored vaginal discharge with backache persisting for 1 month. Gynecologic examination showed severe cervix erosion, papillary protrusion with contact bleeding, and the left uterosacral-cardinal ligament was rigid. According to the cervical biopsy by colposcopy, the patient was diagnosed with cervical moderate differentiated adenocarcinoma invading beneath mucosa. After radical hysterectomy with BSO and PL, she was diagnosed of VGA, staging FIGO IB1, with no evidence of LNM. The patient received adjuvant chemotherapy 2 months later and remained free of recurrence 79 months posthysterectomy.

Case 3: a 39-year-old female (gravida 2, para 1) came to our hospital on February 27, 2015, with complaint of gradually increasing amount of postcoital vaginal bleeding during the past 8 months. Gynecologic examination revealed a 1.0 cm cauliflower-like neoplasm located in the barrel-shaped cervix. The histopathology of cervical biopsy revealed VGA with predominantly exophytic growth pattern and p16 positive. According to the observation of cystoscopy, the cervical tumor protruded to bladder and located near the opening of ureters, indicating that the complete excision would be under the risk of injuring the bladder. The patient underwent BSO with pelvic and periaortic lymphadenectomy, and was finally staged as FIGO IVB with extensive metastasis, including bilateral ovaries, peritoneum, and pelvic LN (1/14). External beam irradiation with precise brachytherapy coupled with chemotherapy was added subsequently. The patient received another 4 cycles of chemotherapy 4 months after the surgery. A positron emission tomography - computed tomography scan detected metastasis to lung and the postoperative pathology suggested infiltrating adenocarcinoma was infiltrating, which was consistent with cervical adenocarcinoma Silva C type. She remains alive after a 61-month follow-up period.

Case 4: a 58-year-old female (gravida 2, para 1) was referred to our hospital on August 3, 2015, because of abnormal vaginal discharge for 6 months, which was light yellow and occasionally mixed with blood. A cauliflower-like neoplasm was shown at the cervix under gynecologic examination. Atypical glandular cell was reported by the following thinprep cytologic test and high-risk human papillomavirus (HPV) infection was detected. An initial

diagnosis of cervical VGA was made based on biopsy, which was supported by immunohistochemistry results with CEA and p16 positive. The patient was finally staged as FIGO IB1 after a radical hysterectomy with BSO and PL. In accordance with the pathologic reports, the invasion of the villoglandular papillary adenocarcinoma was within inner half of the cervical wall, without invading to the endometrium, ovary or oviductus. No lymphovascular invasion (LVI) or LNM was detected. The patient currently shows no evidence of tumor recurrence or metastasis at 56 months postsurgery.

RESULTS

Clinicopathologic Findings

The details of the clinical findings and management of the disease are showed in Table 1. The median age of the patients was 42, with a range of 37 to 58 years old. The most common symptom was abnormal bleeding. Three of the tumors were stage IB, and 1 patient had stage IVB disease. High-risk types HPV infection was detected in 3 patients. As all of the 4 patients were married with no desire for further fertility, radical hysterectomy with BSO plus bilateral PL was performed. Three of them were treated with subsequent adjuvant therapy, except for 1 patient, where no LVI or LNM was detected in the postoperative specimens. Except for the third patient, they are currently alive without evidence of recurrent disease. The follow-up time ranged from 56 to 120 months.

The histologic characters are summarized in Table 2. In accordance with the cervical conization sample of case 1, the tumor was dominantly composed of papillary structure with small cellular papillae bud from the surfaces of the larger ones. Vacuoles of mucin could be observed in the cytoplasm of the lining stratified columnar cells and nuclear polymorphism was mild. In the hysterectomy specimen, only adenocarcinoma in situ could be observed (Fig. 1).

The posthysterectomy specimen of case 2 presented a moderately differentiated cervical adenocarcinoma. The superficial, exophytic portions contained predominantly thin papillae with fibrous central cores, whose epithelia were typically lined by stratified nonmucinous columnar cells. And the nuclear atypia of the cells was mild to moderate. The invasive parts were well-demarcated glands

TABLE 1. Details of Patients' Clinical Characteristics

No.	Age (y)	Reason for Referral	FIGO Stage	HPV Status	LN Status	Treatment	Follow-up (Mo)	Outcome
1	44	Abnormal cervical biopsy	IB1	+(TCT)	-	Radical hysterectomy+bilateral salpingo-oophorectomy +pelvic lymphadenectomy+chemotherapy	120	NED
2	37	Abnormal vaginal discharge with backache	IB1	-	-	Radical hysterectomy+bilateral salpingo-oophorectomy +pelvic lymphadenectomy+chemotherapy	79	NED
3	39	Abnormal vaginal bleeding	IVB	+(TCT)	+	Bilateral salpingo-oophorectomy+pelvic and periaortic lymphadenectomy+chemotherapy+radiotherapy	61	Metastasis
4	58	Abnormal vaginal discharge	IB1	+(TCT)	-	Radical hysterectomy+bilateral salpingo-oophorectomy +pelvic lymphadenectomy	56	NED

FIGO indicates Federation International of Gynecology and Obstetrics; HPV, human papillomavirus; LN, lymph node; NED, no disease detected; TCT, thinprep cytologic test.

TABLE 2. Histologic Characters

No.	Macroscopy	Histopathology			LVI and LNM
		Exophytic Portion	Invasive portion	Cellular Atypia	
1	Papillary protrusion with contact bleeding	Papillary structure with small cellular papillae bud from the surfaces of those larger ones	Expansive growth; adenocarcinoma in situ could be spotted	Stratified columnar cells and nuclear polymorphism was mild	-
2	Polypoid exophytic mass protrusion	Thin and tall papillae	Well-differentiated adenocarcinoma with well-demarcated tumor/stromal interface	Stratified nonmucinous columnar cells	-
3	Cauliflower-like neoplasm at the middle of the entrance of barrel-shaped cervix	Exophytic growth pattern with papillary structures		Stratified columnar epithelial cells with mild to moderate nuclear atypicity	+
4	Cauliflower-like neoplasm	Thick papillae with fibrous stromal core	Showed no desmoplastic stromal response or infiltrative growth pattern	Mild cytologic atypia	-

LNM indicates lymph node metastasis; LVI, lymphovascular invasion.

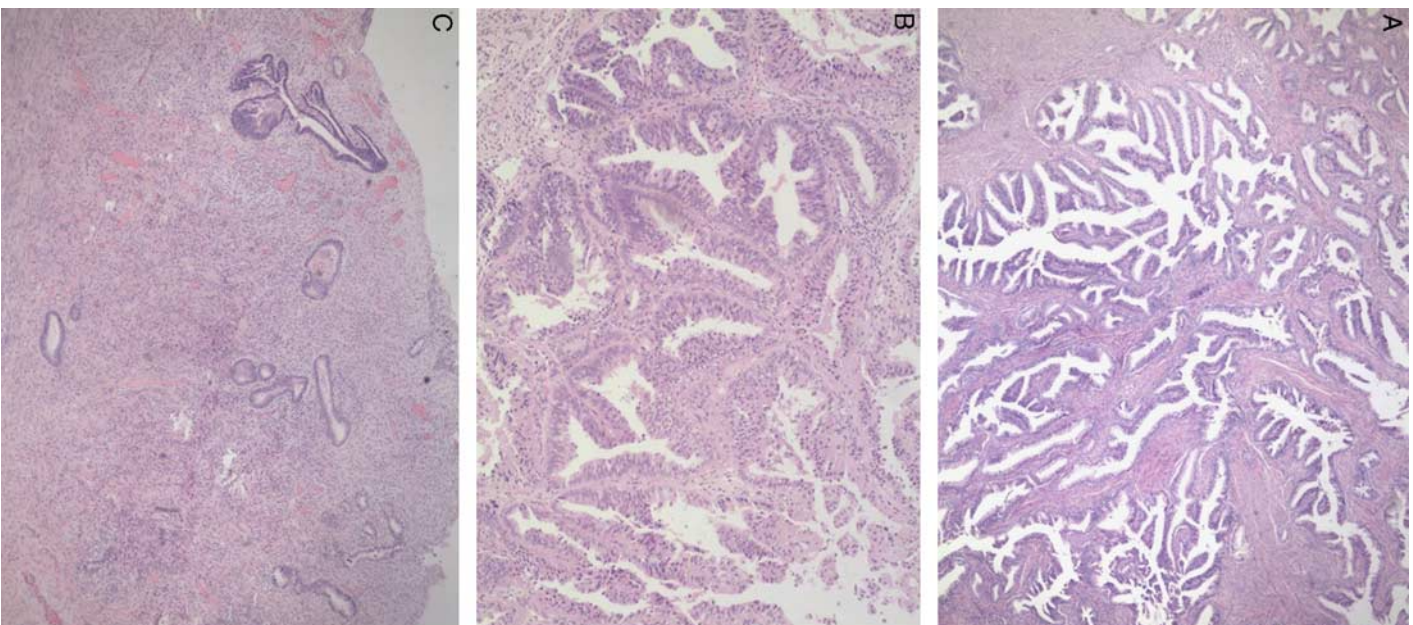


FIGURE 1. Histologic findings of case 1. Hematoxylin and eosin stain, $\times 40$. Papillary structure with small cellular papillae bud from the surfaces of those larger ones (A and B). Adenocarcinoma in situ in the hysterectomy specimen (C).

forming clusters without extensive desmoplastic response (Fig. 2).

As of case 3, only cervical biopsy could be evaluated. The cervical tumors were composed of slim papillary structures arranged in complex branching pattern. Stratified columnar

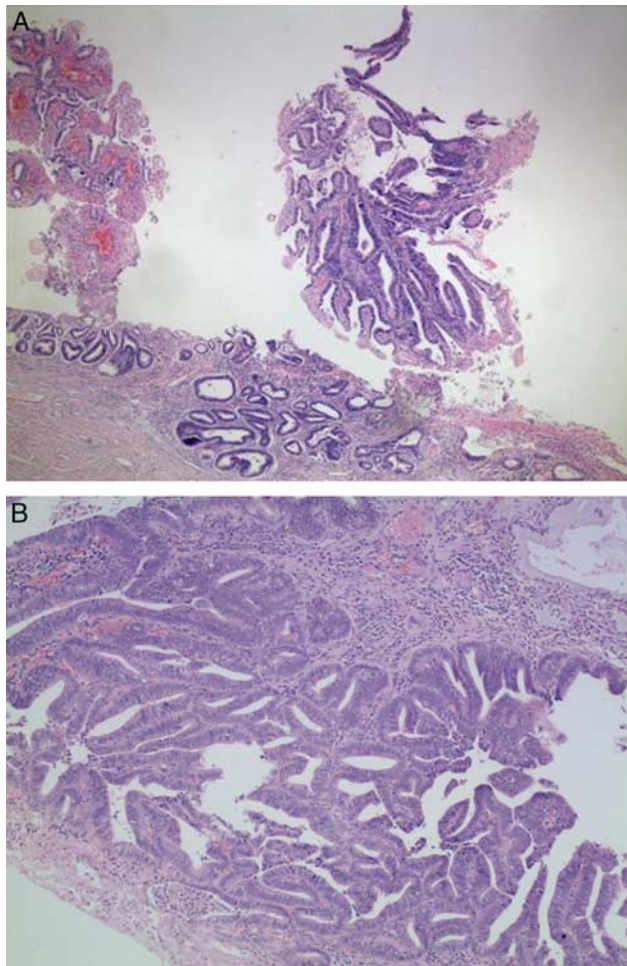


FIGURE 2. Histologic findings of case 2. Hematoxylin and eosin stain, $\times 40$. The exophytic portion of the tumor showed villoglandular pattern and lined by stratified nonmucinous columnar cells (A). The invasive parts were well-demarcated glands forming clusters without extensive desmoplastic response (B). [full color online](#)

epithelial cells covered the papillae were arranged regularly exhibiting mild to moderate nuclear atypicity. The specimen from lung wedge-shaped excision showed infiltrating adenocarcinoma with angulated, canalicular glands (Fig. 3).

The cervical biopsy specimen of case 4 presented thick papillae with inflammatory infiltrating cells in its core. The overlying epithelium showed mild cellular atypia with no solid areas or epithelial tufting. In the hysterectomy specimen, only adenocarcinoma in situ and superficially invasive VGA could be spotted. The superficial elements contained predominantly thin papillae, and the infiltrating components showed no desmoplastic stromal response or infiltrative growth pattern. LVI was not seen (Fig. 4).

DISCUSSION

VGA of the uterine cervix is relatively rare. From the first 13 cases reported by Young and Scully in 1989,⁴ a

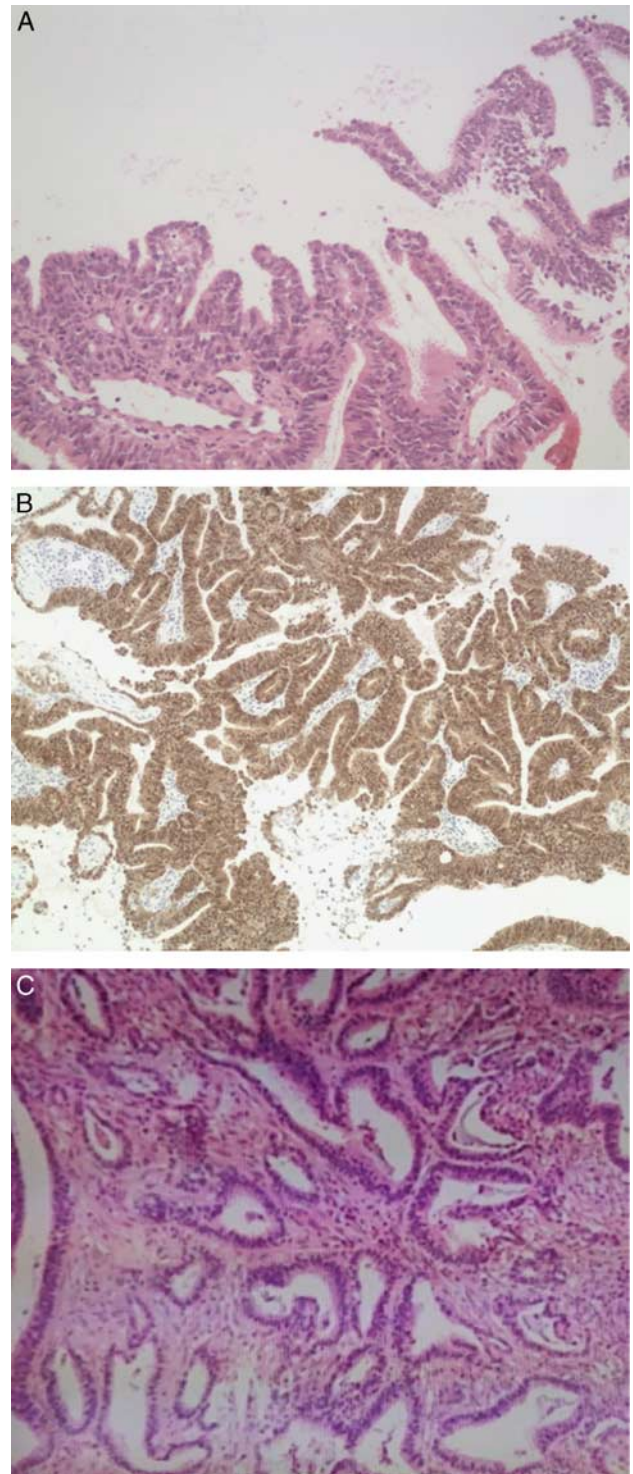


FIGURE 3. Histologic and immunohistochemical findings of case 3. Hematoxylin and eosin stain, $\times 200$ (A); immunohistochemistry, $\times 100$ (B). Slim papillary structures (A). Diffuse p16 staining positivity (B). The metastatic lesion showed irregular and angulated glands corresponding to Silva (C). [full color online](#)

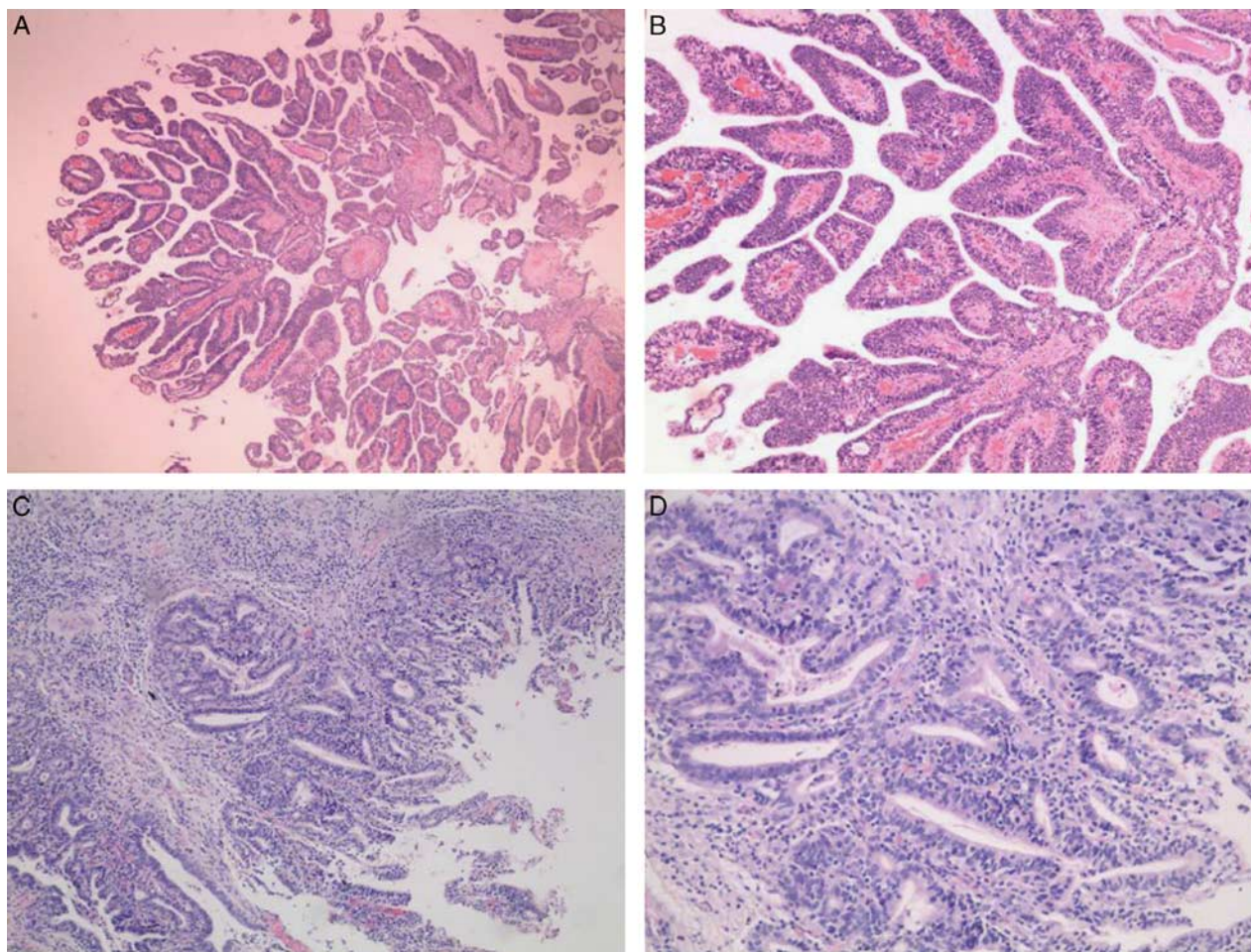


FIGURE 4. Histologic findings of case 4. Hematoxylin and eosin stain, $\times 40$ (A), $\times 100$ (B and C), $\times 200$ (D). The cervical biopsy specimen presented thick papillae with fibrous stromal core (A&B). In the hysterectomy specimen, the superficial elements contained predominantly thin papillae, and the infiltrating components showed no desmoplastic stromal response or infiltrative growth pattern (C). The overlying epithelia showed mild cytologic atypia (D). [full color online](#)

total of 150 cases have been globally published according to our review of literature. It has arisen attention because of its early onset age, exophytic histologic feature, indolent growth pattern and favorable prognosis.

Compared with other malignant cervical tumors, VGA tend to occur in younger women, particularly those of reproductive age.¹¹ The average age of the total 150 VGA cases was 37, and 83.9% of the patients were under 50. In this series, the median age of patients was 42 with a range of 37 to 58 years.

The etiology of VGA is still obscure. HPV infection, particularly high-risk types, in the role of molecular pathogenesis of VGA has been put forward,¹² and high-risk types HPV were indeed detected in 3 of our 4 patients. In 1993, Jones et al⁶ proposed a possible relationship between VGA and oral contraceptives (OC) usage. This view was supported by the study of Ursin et al¹³ in which he found the history of taking OC doubled the risk of adenocarcinoma of the cervix (adjusted odds ratio: 2.1; 95% confidence interval: 1.1-3.8). However, no history of OC usage history was found in our patients.

On gross examination, a large majority of the VGA presented as friable, papillary or polypoid masses or cervical cauliflower-like exophytic lesions. But occasionally there are infiltrative and friable lesions.¹³ In our cases, 2 of the neoplasms were presented in cauliflower-like pattern. And deeper infiltration with parametrial extension was examined in the third case.

The major features of VGA were exophytic proliferation, papillary architecture and mild to moderate cellular atypia. In our cases, the superficial, exophytic portion of the tumor was composed of variably sized papillary and villous fibrovascular fronds, which were typically lined by stratified nonmucinous columnar cells with only mild nuclear atypia and increased mitotic activity. As far as the invasion part was concerned, regardless of the invasion depth achieved by tumor cells, they were predominantly well-demarcated glands frequently forming clusters or groups and sometimes showing relatively well-preserved lobular architecture.

Currently, although it is the size and depth of invasion of the tumor that largely determines stage and prognosis of the patients with endocervical adenocarcinoma in clinical

practice,¹⁴ histologic architectures and growth patterns may indicate the malignancy potential of tumors as well, and VGA is a good paradigm. A new classification system for invasive endocervical adenocarcinomas based on pattern of invasion, namely Silva system, was put forward in 2015.¹⁵ The growth pattern of VGA is in highly concordance with pattern A of Silva system, which is composed by well-demarcated glands with rounded contours, without destructive stromal invasion or cell detachment.¹⁵ On the basis of the multicenter clinical studies, patients with Silva system pattern A cervical adenocarcinomas rarely had LN metastasis and recurrence. Therefore, LN dissection could be avoided.¹⁵ Given that VGA frequently occur in young women of reproductive age, it has been suggested that less invasive surgical treatment without adjuvant radiation therapy, including local excision with cold knife cone or extrafascial hysterectomy could be performed in patients presented as pattern A of Silva system.¹⁶

However, it should be noted that, according to the statistics of our reviewing of English literature, 4.2% of VGA cases could be associated with other invasive patterns, including: poorly differentiated infiltrating adenocarcinoma,⁹ squamous cell carcinoma,^{17–19} and small cell carcinoma.²⁰ Therefore, Korech et al²¹ suggested that the diagnosis of VGA should be made only after the tumor had been completely excised. In case 3, even though an exophytic growth pattern and only superficial invasion of the cervical wall was showed in biopsy specimen, bladder involvement, and pelvic LNM indicated that there might be aggressively growth pattern in deeper cervical wall. Moreover, pelvic LNM and parametrial invasion are considered to be high-risk factors for recurrence.¹⁰

Molecular mechanism underlying the indolent biologic behavior of VGA is still unknown. On the basis of the study 12 cases of VGA, Jones et al²² confirmed the crucial role of HPV infection (mainly type 16 and 18) in the pathogenesis of VGA, and indicated the indolent biologic nature of this neoplasm, given the fact that neither the loss of tumor suppressor gene (*p-53*, *MCC*, *APC*, and *BRCA1*) nor the amplification of oncogene (*c-erb-B2/neu* and *int-2*) was detected. It is supported by the Silva system has presented that the invasive growth pattern of the endocervical adenocarcinomas would largely determine its clinical prognosis. And cancer invasion is initiated and maintained by signaling pathways that control cytoskeletal dynamics in tumor cells and the turnover of cell-matrix and cell-cell junctions, followed by cell migration into the adjacent tissue.²³ Featuring by an expansive growth pattern, VGA form a multicellular outward pushing with intact cell-cell junctions and no signs of destruction of the extracellular matrix, which would attribute to its inert migration. Therefore, to illuminate the driven pathway orchestrating those distinct features of VGA, we plan to further investigate the molecular pathways underlying the growth pattern of VGA and mechanism by which normal and neoplastic cells migration within extracellular matrix.

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