BRIEF COMMUNICATION

The clinicopathologic and immunohistochemical features of villoglandular adenocarcinoma of uterine cervix

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ABSTRACT

Aim: Villoglandular adenocarcinoma (VGA) of the uterine cervix is a variant of endocervical adenocarcinoma. However, the clinicopathologic and immunohistochemical features of VGA are still unclear. The aim of this study was to investigate the clinicopathologic and immunohistochemical features of VGA. **Materials and Methods:** A total of 20 VGA patients were identified among 852 patients diagnosed with cervical cancer and enrolled in this study. The immunohistochemical levels of Ki-67, P53, P16, progesterone receptor (PR), carcinoembryonic antigen (CEA), vimentin (Vim), and estrogen receptor (ER) were measured by immunohistochemistry. **Results:** VGA was prevalent in younger women and presented favorable prognosis. Ki-67, P16, and CEA were highly expressed in VGA tissues, while PR expression was hardly to be detected. The positive rates of Ki-67, CEA, and P16 were 90.0%, 90.0%, and 85.0%, respectively, which were significantly higher compared with PR (5.0%, $P < 0.001$). In addition, the positive rates of P53, Vim, and ER in VGA tissues were 55.0%, 50.0%, and 40.0%, respectively. However, the expression levels of Ki-67, P53, P16, PR, CEA, Vim, and ER were not significantly associated with clinical features ($P > 0.05$). **Conclusion:** These data indicate that VGA is a rare cervical adenocarcinoma, which is prevalent in younger women, and presents favorable prognosis. Detection of Ki-67, P53, P16, PR, CEA, Vim, and ER would be beneficial for the diagnosis of VGA.

KEY WORDS: Clinical stage, clinicopathologic feature, human papillomavirus infections, outcome, villoglandular adenocarcinoma

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INTRODUCTION

Villoglandular adenocarcinoma (VGA) of the uterine cervix is first described by Young and Scully in 1989.[1] VGA is identified as a variant of endocervical adenocarcinoma and presented a distinct exophytic and villous-papillary growth pattern.[2,3] Compared to other cervical malignant tumors, VGA tends to occur in younger women and is rarely to involve in vascular space and lymphatic metastasis.[4-6]

In addition, current studies reported that if no residual disease and vascular space involvement were found in the cone margins, it would be acceptable for VGA patients to preserve fertility without further treatment.[7,8] However, the underlying etiopathogenesis and diagnostic criteria of VGA are unclear. Although human papillomavirus (HPV) is reported to be involved in the pathogenesis of VGA,[9-11] immunohistochemical feature of VGA remains unclear. In this study, we investigated the immunohistochemical levels of Ki-67, P53, P16, progesterone receptor (PR), carcinoembryonic antigen (CEA), vimentin (Vim), and estrogen receptor (ER) in 20 cases of

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VGA tissues and also analyzed the clinicopathologic feature of VGA.

MATERIALS AND METHODS

Patients

Between 2010 and 2016, 852 patients with cervical cancer were treated in our hospital. Twenty patients (2.3%) who received pretreatment biopsy or posttreatment pathology were confirmed to be VGA and enrolled in this study. Patients with other types of adenocarcinoma or only villoglandular patterns were excluded. Clinical data were obtained from hospitalization note, including age, clinical stage (based on the International Federation of Gynecology and Obstetrics [FIGO]), management, outcome, and follow-up.

Hematoxylin and eosin staining

Tissues were fixed with 4.0% formaldehyde. Two-micrometer sections were cut from paraffin blocks and placed on glass slides. Sections were deparaffinized with xylene and graded ethanolthe. Then, sections were stained with hematoxylin and eosin (H and e).

Immunohistochemistry

Immunohistochemical staining was performed as described previously.[12,13] Two-micrometer sections were cut from paraffin blocks and placed on glass slides. Sections were deparaffinized with xylene and graded ethanolthe, and endogenous peroxidase activity was repaired by 0.01 M sodium citrate buffer (pH 6.0). Monoclonal mouse anti-human Ki-67, P53, P16, PR, CEA, Vim, and ER were used as primary antibodies. After incubation for 2 h at room temperature, sections were washed with phosphate-buffered saline with and incubated with secondary biotinylated antibody for 30 min at room temperature. Finally, sections were flooded with diaminobenzidine tetrahydrochloride and stained with hematoxylin. Normal rabbit or mouse immunoglobulin was used to replace primary antibody in negative controls. These tissues reported to be positive expression were regarded as positive controls.

Statistical analysis

All results were analyzed with SPSS 19.0 (SPSS, Chicago, IL, USA). The comparison of Ki-67, P53, P16, PR, CEA, Vim, and ER in VGA tissues was performed by the Chi-square test. $P < 0.05$ was defined as a statistical significance.

RESULTS

A total of 20 VGA patients were identified among 852 patients diagnosed with cervical cancer, which accounted for 2.3% (2.3/852) incidence of cervical cancer. The median age of patients was 40 years with a range from 28 to 54 years. Among 20 patients, 14 (70.0%) patients presented abnormal vaginal bleeding, 12 (60.0%) patients received abnormal liquid-based cytology, and 8 (40.0%) patients presented positive expression of HPV 16. After completed cervical biopsy, 16 patients received radical hysterectomy with pelvic lymphadenectomy and 4 patients received radical hysterectomy without pelvic lymphadenectomy. While no lymphovascular space invasion was observed in VGA patients before surgery. Based on the International FIGO, 13 patients belonged to Stage I_B, 5 patients were Stage II_A, and 2 patients were stage II_B. After surgery, 14 patients received chemotherapy (CT) and pelvic radiotherapy (PT) and 6 patients only received PT. Histopathologically, cytological atypia was minimal. H and E staining showed that complex branching villous-papillary architecture and the stratified lines were covered by tall, endocervical-type columnar cells with limited abnormal mitotic figures [Figure 1a]. Follow-up time was ranged from 16 to 70 months with a median of 45 months. All patients were alive, and 1 (5.0%) patient suffered from recurrence in the 3rd year after surgery. Overall survival and 5-year disease-free survival were 100% and 95.0%, respectively.

Then, we detected the expression levels of Ki-67, P53, P16, PR, CEA, Vim, and ER in VGA tissues by immunohistochemistry (IHC). Results shown that Ki-67, P16, and CEA were highly expressed in VGA tissues [Figure 1b-d], while PR was hardly to be detected [Figure 2a]. The positive rates of Ki-67, CEA, and P16 were 90.0%, 90.0% and 85.0%, respectively, which were significantly higher compared with PR (5.0%, $P < 0.001$). In addition, positive expression of P53, Vim, and ER was also observed in VGA tissues [Figure 2b-d]. The positive rates of P53, Vim, and ER were 55.0%, 50.0%, and 40.0%, respectively. However, the expression levels of Ki-67, P53, P16, PR, CEA, Vim, and ER were not significantly associated with clinical features in VGA patients ($P > 0.05$).

DISCUSSION

VGA is one of uterine cervical adenocarcinomas, which is extremely rare to be reported worldwide.[14,15] Compared with

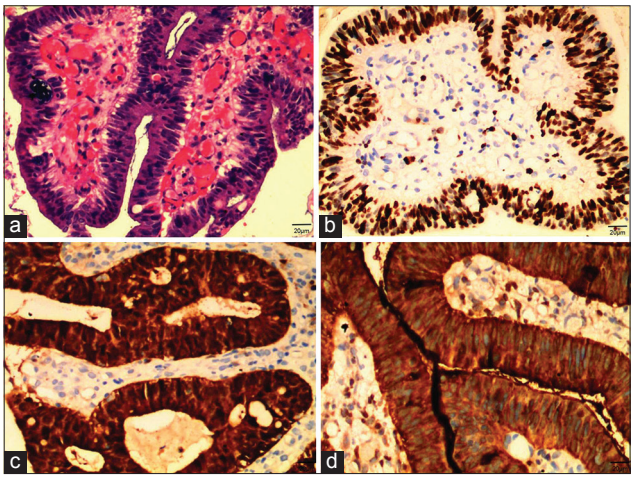

Figure 1: H and E staining and immunohistochemical levels of Ki-67, P16, and carcinoembryonic antigen in villoglandular adenocarcinoma tissues. (a) H and E staining of villoglandular adenocarcinoma tissues. (b) Ki-67 was highly expressed in villoglandular adenocarcinoma tissues. (c) P16 was highly expressed in villoglandular adenocarcinoma tissues. (d) Carcinoembryonic antigen was highly expressed in villoglandular adenocarcinoma tissues

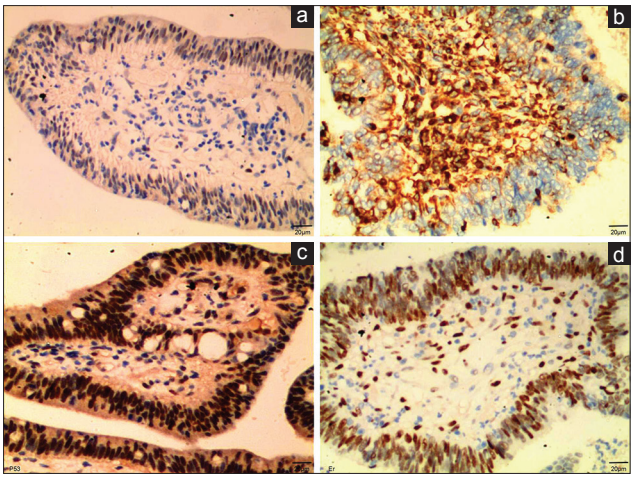

Figure 2: The expression of progesterone receptor, P53, vimentin, and estrogen receptor was detected in villoglandular adenocarcinoma tissues by immunohistochemistry. (a) Progesterone receptor was hardly detected in villoglandular adenocarcinoma tissues. (b) Vimentin was highly expressed in villoglandular adenocarcinoma tissues. (c) P53 was highly expressed in villoglandular adenocarcinoma tissues. (d) Estrogen receptor was highly expressed in villoglandular adenocarcinoma tissues

other cervical adenocarcinoma, VGA is most prevalent in younger women. Young and Scully[1] firstly reported 13 cases of VGA with an average age of 33 years. Lataifeh *et al*.[16] reported 28 cases with a mean age of 38 years. However, the mean age of VGA patients in this study was 40 years with a range from 47 to 70 years. Clinically, nonspecific manifestations were observed in VGA patients, and abnormal vaginal bleeding, postcoital bleeding, and abnormal vaginal discharge were commonly observed in the majority of cases.[16] In the present study, 14 (70.0%) patients presented abnormal vaginal bleeding. Studies reported that HPV infection was associated the pathogenesis of VGA.[9-11] Our study shown that 40.0% of patients presented positive expression of HPV 16, which further supported the correlation between HPV infection and VGA. Until now, radical hysterectomy with lymph node dissection and radiotherapy are considered as the best treatment for invasive adenocarcinoma.[17] However, favorable prognosis was widely recorded in VGA patients. If no residual disease and vascular space involvement were found in the cone margins, it would be acceptable for VGA patients to preserve fertility without further treatment.[7,8] In this study, 16 patients received radical hysterectomy with pelvic lymphadenectomy and 4 patients received radical hysterectomy without pelvic lymphadenectomy. After surgery, 14 patients received both CT and PT and 6 patients only received PT. While all patients were alive during the last time of follow-up, which suggested CT and PT might be not needed after surgery.

As the diagnostic accuracy of cervical biopsy is lower, the diagnosis of VGA is mainly depended on the final histological pathology.[18] Meanwhile, histopathologic diagnosis is difficult for VGA because 30% of VGA occurs with other types of invasive cancer.[19-21] Therefore, immunohistochemical features of VGA might be beneficial for the diagnosis. In this study, we detected the immunohistochemical levels of Ki-67, P53, P16, PR, CEA, Vim, and ER by IHC. High expression of Ki-67, P16, and Vim is reported to be associated with the recurrence and unfavorable prognosis in cervical cancer.[22-24] P53 is reported to be mutated in 66% of cervical carcinomas, and mutated P53 protein in nucleus predicts better prognosis.[25] The levels of ER, PR, and CEA are reported to be correlated with cervical cancer therapy.[26-28] Our data showed that Ki-67, P16, and CEA were highly expressed in VGA tissues, and the positive rates were 90.0%, 90.0%, and 85.0%, respectively. However, PR was hardly detected in VGA, and the positive rate was only 5.0%. Positive expression of P53, Vim, and ER was only observed in part of VGA tissues. These data indicated that detection of Ki-67, P53, P16, PR, CEA, Vim, and ER was beneficial for assessing the diagnosis of VGA. However, the expression levels of Ki-67, P53, P16, PR, CEA, Vim, and ER were not significantly associated with clinical features in VGA patients, which might be caused by the small sample size. Thus, further investigation with larger sample size would be more valuable. However, it is very difficult to obtain tissue samples because of lower incidence of VGA.

CONCLUSION

Our data further validate that VGA is a rare cervical adenocarcinoma, which forecasts favorable prognosis. Detection of Ki-67, P53, P16, PR, CEA, Vim, and ER may be beneficial for the diagnosis of VGA.

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Conflicts of interest
There are no conflicts of interest.

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