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Four cases of villoglandular papillary adenocarcinoma and literature review.

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Abstract

Objective: To explore the clinical and pathological features, diagnosis and therapy of Villoglandular Papillary Adenocarcinoma (VGPA).

Methods: 4 cases of villoglandular papillary adenocarcinoma of uterine cervix admitted from 2001 to 2009 in Children's Hospital, Shanxi Provincial People's Hospital were analysed retrospectively, including detailed clinical data.

Results: (1) Most of the tumors were extrinsic type, growing slow, no specificity in clinical manifestations, which were found in the early stage generally. (2) 3 cases were infected by high risk Human Papilloma Virus (HPV), 2 of them were mixed infection, and the FIGO stages were all Ib. (3) The preoperative pathological examinations of 3 cases were inconsistent with the postoperative ones. (4) The postoperative pathological examinations showed that there were different degrees of myometrial invasion, but no lymphatic and vascular metastasis. Immunohistochemical staining showed that *CK7*, *CA72-4*, *CEA*, *CA125* and *P16* expression were positive in tumor tissues, but *ER*, *PR*, *P53* and *Vimentin* were negative. (5) One of 4 cases received total hysterectomy and radiotherapy after surgery, and the others accepted wide hysterectomy and pelvic lymph node dissection, but no radiotherapy after operation. All patients were followed up till now, no recurrence.

Conclusion: (1) High risk HPV may play a role in the pathogenesis of VGPA. (2) It is difficult to diagnose before surgery only by clinical and routine pathological examination, but combined with immunohistochemistry may help to improve the preoperative diagnosis rate of VGPA. (3)The prognosis may be good, but the lesion is easy to invade the muscle layer, so conservative surgery need to be chosen carefully.

Keywords: Uterine cervix, Villoglandular papillary adenocarcinoma, Cervical neoplasia, Immunohistochemistry.

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Introduction

Villoglandular Papillary Adenocarcinoma (VGPA), also named Villoglandular Adenocarcinoma (VGA), refers to a rare well-differentiated adenocarcinoma of uterine cervix. At present, there are only 8 cases reported in the Chinese literature [1-7]. In 1994, it was classified as the pathological type of cervical cancer by WHO in 1994, which is a subtype of cervical adenocarcinoma. Now the clinical and pathological features, diagnosis, therapy and follow-up data of 4 VGPA cases admitted from 2001 to 2015 in our hospital are generalized, meanwhile, they are tested immunophenotype of the tumor with immunohistochemistry retrospectively, and combined with the relevant literature, the analysis is following.

Data

From January 2001 to October 2015, 4 VGPA cases were admitted in the Children's Hospital, Shanxi Provincial People's Hospital, meanwhile, there were 53 cases of cervical cancer totally in the hospital, accounted for 7.55% (4/53).

The first case was 50 years old, married at 21 years old, G2P2, no history of oral contraceptives and smoking. In July 2007, due to little vaginal bleeding after sex, the patient visited the doctor in the Second People's Hospital of Wenzhou and received cervical biopsy. The pathology showed that: severe chronic cervical inflammation, accompanied by low Cervical Intraepithelial Glandular Neoplasia (CIGN), focal area cervical intraepithelial moderate-severe dysplasia, and small focal Cervical Intraepithelial Neoplasia (CIN) I-II grade. She was transferred to our hospital in July 18, 2007, admitted in our hospital with a consideration of cervical CINII-III grade. Gynecological examination showed that: the vulva and vagina were normal, but there was papillary vegetation about 1.5 × 1.5 cm in size located at six o'clock of cervix, easy bleeding. After preoperative preparation, the patient underwent simple total hysterectomy. The gross specimen showed: Vegetation located

at six o'clock of cervix was about 1.5 × 1.5 cm in size, which could be seen to invade the shallow muscle layer, what's more, there was a polypoid about 1.5 × 1.5 cm in size in the cavity of uterus. Postoperative pathological examination showed that: it was VGPA, invaded 2/3 of the cervical wall, but unaffected the cervical canal and the endometrium was secretory one, accompanied by endometrial polyps. Immunohistochemical staining was performed on paraffin sections of cervical masses for *CK7*, *CA72-4*, *CEA*, *CA125*, *P16*, *ER*, *PR*, *P53* and *Vimentin*. *CK7*, *CA72-4*, *CEA*, *CA125* and *P16* expression were positive in tumor tissues, but *ER*, *PR*, *P53* and *Vimentin* expression were negative. The types of HPV *in situ* hybridization (6/11, 16/18, 31 and 33) were all negative. Due to the lesion invaded 2/3 of the cervical wall, the patient accepted external radiotherapy after surgery. And follow-up had been 34 months till now, no recurrence.

The second case was 52 years old, married at 21 years old, G4P3, no oral contraceptives and smoking history. In June 2006, the patients received subtotal hysterectomy due to hysteromyoma in our hospital. The cervical examination before operation showed no disorder, and the patient didn't review after surgery. She reviewed in the Maternal and Child Health Hospital of Leqing in May 4, 2009, and the Thin-prep Cell Test (TCT) showed there were atypical squamous cells, then she underwent cervical biopsy with vaginoscope, of which pathological result indicated that it was endometrioid and well-differentiated papillary adenocarcinoma of cervix and chronical mucositis of cervix. She was transferred to our hospital in May 21, 2009, admitted with a consideration of cervical adenocarcinomas Ib grade. Gynecological examination at admission showed normal vulva, smooth vagina, and a cauliflower-like vegetation about 3 × 3 cm in size located at nine o'clock of cervix. The examination of HPV had 16 type positive. After preoperative preparation, the patient underwent wide amputation of cervix and lymph node dissection. The gross specimen showed: Cauliflower-like vegetation located at nine o'clock of cervix was about 3 × 3 cm in size, which could be seen to invade the shallow muscle layer. Postoperative pathological examination showed that: it was VGPA, invaded the shallow muscle layer of cervix, but no lymphatic and vascular metastasis. Immunohistochemical staining showed that *CK7*, *CA72-4*, *CEA*, *CA125* and *P16* expression were positive, but *ER*, *PR*, *P53* and *Vimentin* expression were negative. And follow-up had been one year till now, no recurrence.

The third case was 70 years old, married at 17 years old, G6P6, no oral contraceptives and smoking history. The patient had got vaginal hemorrhage for half a year, which was white, thin and moderate, accompanied by low abdominal discomfort, so she visited the doctor in the local people's hospital and accepted cervical biopsy. The pathological diagnosis was papillary adenocarcinoma, and then the patient was transferred to our hospital, admitted with a consideration of cervical adenocarcinomas. Gynecological examination showed papillary vegetation about 1.5 × 1.0 cm in size located at twelve o'clock of cervix. After admission, the patient underwent wide hysterectomy and bilateral salpingo-oophorectomy and pelvic lymph node dissection. The gross specimen showed papillary vegetation about 1.5 × 1.0 cm in size located at twelve o'clock of cervix, and smooth cervical canal. Rapid frozen section in the operation indicated that it was VGPA. Postoperative paraffin section showed it was VGPA invaded the shallow muscle layer of cervix, accompanied by endometrium invasion, but no tumor in the intimal of cervical canal and resection margin of vagina, and no pelvic lymphatic and vascular metastasis. Immunohistochemical staining showed that *CK7*, *CA72-4*, *CEA*, *CA125* and *P16* expression were positive, but *ER*, *PR*, *P53* and *Vimentin* expression were negative. The types of HPV *in situ* hybrization (6/11, 16/18, 31 and 33) were strong positive. And follow-up had been performed till now, no recurrence.

The forth case was 47 years old, married at 23 years old, G2P2, no oral contraceptives and smoking history. Due to postcoital bleeding three years ago, which was little and red, she visited the local hospital, diagnosed as endometritis, and took some medicine, but no marked recovery. After that, the patients suffered from postcoital bleeding repeatedly. She visited our hospital in August 10, 2009, and gynecological examination indicated cervical vegetation, so she underwent a cervical biopsy with vaginoscope immediately. The pathology reported that it was VGPA, and HPV examination indicated that 16, 56 and 66 types were positive. With a diagnosis of VGPA Ib grade, she was admitted in our hospital. After admission, she underwent wide hysterectomy and pelvic lymph node dissection. Postoperative pathology indicated that it was VGPA invaded the shallow muscle layer of cervix, but no pelvic lymphatic and vascular metastasis. Immunohistochemical staining showed that *CK7*, *CA72-4*, *CEA*, *CA125* and *P16* were positive, but *ER*, *PR*, *P53* and *Vimentin* were negative. And follow-up had been 8 months till now, no recurrence.

Discussion

VGPA is a rare type of cervical adenocarcinoma. Since 1989, Young and Scully [8] firstly described and proposed it, there are nearly 100 cases reported at home and overseas. Since Sun [1] reported the first case in China in 2002, there are only 8 cases. Due to VGPA is rare and most of them are case reports, it lacks enough knowledge about its clinical and pathological features, so mistake diagnose rate before surgery is higher. Therefore, increasing the knowledge about VGPA is necessary, aiming to improve its diagnosis and therapy.

Etiologies of VGPA isn't clear, some literature reports that it may relate to smoke, oral contraceptives, and high risk HPV (16 and 13 type) [9]. All 4 cases in this paper have no history of oral contraceptives and smoke, but 3 of them are infected with HPV, mainly HPV16, 2 among them are infected with several high risk HPV, respectively HPV16, 18, 31 and 33, and HPV16, 56 and 66. High detection rate of high risk HPV in patients with VGPA indicates it may play a role in pathogenesis of VGPA.

VGPA usually occurs in young female, resulting in a median age at onset of 33~38 years, according to the report, the youngest was 22 years old [10]. 4 patients in this paper are 47, 50, 52 and 70 years old respectively, and the patient who is 70 years old is the oldest one at onset in the reports of domestic and overseas so far. Clinical manifestations of VGPA have no specificity, and most of them are diagnosed at early stage. Among 4 cases, two have postcoital bleeding, and one vaginal hemorrhage. The appearance of vagina shows polyp or papillary vegetation or erosion mostly. However, extrahepatic growing of VGPA causes that its clinical manifestations appear earlier, or it is easy to be found in gynecological examination. All 4 cases show extrahepatic growing.

The tumor generally manifests as polyp or papillary vegetation or erosion which can be seen, and grows toward the external mainly. Observed by microscope, the tumor consists of complex villus papillary structures, covering the vagina epithelium, endometrium or intestinal epithelium, with mild-moderate atypical hyperplasia of nucleus and mitotic count increasing. Its histology manifestation is similar to villous adenoma of colon and rectum, and some cases are accompanied by adenocarcinoma *in situ* or CIN. What's more, it may coexist with other type of tumor cells (squamous cell carcinoma). The pathological diagnosis of VGPA focuses on the villus structure observed by microscope more. At present, only the whole or most tumor tissues (>90%) consist of villoglandular structure can it be diagnosed as VGPA [8,11].

Due to its cytohistological characteristics, just based on cytologic examination of cervical smears results in missed diagnosis easily [12]. What's more, because of less or shallower biopsy specimens before surgery, only relying on cervical biopsy to make a diagnosis and treatment protocols directly is improper [13], which lead to more difficulty in preoperative diagnosis and higher rate of misdiagnosis or missed diagnosis . After analysing the pathologies of twelve cases which were diagnosed as VGPA before surgery, Jacob [14] found that 9 cases were confirmed, among them, only 2 had consistent diagnosis before and after surgery, 3 were diagnosed as benign or precancerous lesion preoperatively, and 4 invasive malignant tumors. This study has 4 cases, but only one has consistent diagnosis before and after surgery, and the others don't. The first case was diagnosed as severe chronic cervical inflammation accompanied by low Cervical Intraepithelial Glandular Neoplasia (CIGN), foci cervical intraepithelial moderate-severe dysplasia, and small foci Cervical Intraepithelial Neoplasia (CIN) I-II grade. The pathological diagnosis of postoperative samples in our hospital is VGPA, invaded 2/3 of the cervical wall. Through pathological consultation with the preoperative section of the other hospital, and performing immunohistochemical staining on the specimens of cervical mass, it is confirmed as VGPA. The pathological results before surgery of the other two cases (the second and third) are well-differentiated papillary adenocarcinoma. The high misdiagnosis rate before surgery may be related to more local biopsy specimens before operation without the invasive focus of basilar part. What's more, due to its uncommon, some pathological workers are lack of the knowledge about it, which causes high misdiagnosis or missed diagnosis rate before operation. The paraffin sections of cervical masses of 4 cases are detected for *CK7*, *CA72-4*, *CEA*, *CA125*, *P16*, *ER*, *PR*, *P53* and *Vimentin* expression of the tumor through immunohistochemistry in the study, and all tumor tissues of 4 cases express *CK7*, *CA72-4*, *CEA*, *CA125* and *P16*, indicating cervical carcinoma *in situ* [15-18], but no *ER*, *PR*, *P53* and *Vimentin*, excluding endometrial carcinoma invaded the cervical canal [16-19]. Therefore, combining tissue pathological section with immunohistochemistry to detect *CK7*, *CA72-4*, *CEA*, *CA125* and *P16* may improve its preoperative diagnosis rate.

There is still a controversy on the treatment of VGPA. Previous literature reported [15] that the therapies of VGPA includes conization of cervix, simple hysterectomy, wide hysterectomy (and/or pelvic lymph node dissection) and preoperative and postoperative radiotherapy. Most of them claimed that the well differentiated VGPA have good prognosis, predicting the feasibility of conservative surgery [13]. Young [8] held that for the patients, who have birth demand, with tumor which has no lesion at the resection margin, invasive depth<3 mm without affected the lymph canal, conization of cervix should be the first choice. About the selection of operation types, Hoffman etc. [16] thought that for VGPA with the invasive depth of tumor less than 3mm and no lymphatic metastasis, if conservative surgery will be implemented, partial amputation of cervix may be better than conization of cervix. Utsugi et al. [11] claimed that according to the literature of VGPA, the rate of lymphatic vessel invasion and lymphatic metastasis is very low, so operators select conservative surgeries, such as conization of cervix. But for the patients with high risk factors of pathology, treatment protocols should be made more careful. Other scholars proposed [17] that bad factors affecting the prognosis should be evaluated attentively before conservative surgery. Apart from VGPA, there may be some other type of tumor cells at the same moment, and these cells may predominate. In this instance, the rationality of conservative surgery should be considered. All 8 cases reported in China underwent total hysterectomy, follow-up for 1~2 years, no recurrence. Lymphatic vessel and interstitial invasion may be the high risk factors of lymphatic metastasis for well differentiated VGPA [10]. Postoperative adjuvant radiotherapy should be given to the patients with lymphatic metastasis. Khunamornpong [10] said that the patients with lymphatic metastasis who received postoperative radiotherapy were followed up for 21~144 months (67.5 months in average), but no recurrence. Some scholar reported one case with IIb grade. The patient underwent wide hysterectomy and pelvic lymph node dissection and bilateral salpingo-oophorectomy, and the postoperative pathology indicated lymphatic metastasis, so she received postoperative radiotherapy. Finally, the patient had lived for 17 years without tumor [18]. However, some of the patients with lymphatic metastasis dead, even they accepted postoperative radiotherapy [15-19]. The postoperative pathologies of all 4 cases in the study show cervical muscle layer invasion, but no lymphatic and vascular metastasis.

VGPA is deemed that it invades the muscle layer easily, so the choice of conservative surgery should be made cautiously.

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