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Case report

Villoglandular Papillary Adenocarcinoma of the Uterine Cervix with Aggressive Clinical Course – A Case Report

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A B S T R A C T

Villoglandular papillary adenocarcinoma (VGA) of cervix is an uncommon but well recognized histologic subtype of cervical adenocarcinoma which usually affects young women. Based on the favorable outcomes reported in most previous cases the tumor is generally considered to have an indolent clinical course with excellent prognosis. We present a case of a 22-year-old woman admitted at our Department for glandular abnormality on cervical smear and episodes of vaginal discharge. In the Pap smear, the cytological features were suspicious but not diagnostic of adenocarcinoma, therefore reported as atypical glandular cells (AGC). Histological examination confirmed VGA associated with lymphovascular space invasion. The patient underwent radical operative procedure. Intraoperative cytologic examination detected pelvic lymph nodes metastasis. The patient was confirmed to be in an advanced stage – III B (FIGO). During a two years follow-up period a rapid dissemination of the tumor occurred and resulted with a fatal outcome. Although VGA has been reported to have a favorable prognosis, several cases with lymph node involvement have already been described. Cervical smears examination would be helpful for an early diagnosis of VGA, however the cytologic recognition is often difficult. Further investigation of the pathogenesis, diagnosis and therapy of the tumor is needed.

***Key words**: cervical cancer, villoglandular adenocarcinoma, cervical cytology*

Introduction

Recent studies have reported that the incidence of cervical adenocarcinoma has increased in young women over the last several decades. The cause of this increase is unclear, but it is of concern since studies have shown a poorer prognosis for patients with cervical adenocarcinoma than for those with squamous cell carcinoma[1]. Different studies have suggested a linkage of invasive cervical adenocarcinoma with several risk factors including human papillomavirus (HPV) infection, oral contraceptive use and obesity[2,3].

Villoglandular papillary adenocarcinoma (VGA) of the cervix has been identified as a distinct subtype of cervical adenocarcinoma that occurs in young women and generally carries an excellent prognosis[4]. On the other hand, several authors have reported cases of VGA associated with lymphovascular invasion and lymph node affection that were complicated by recurrence and metastasis[5,6]. We present a case of VGA in a young woman with rapid disease spread.

Case Report

A 22-year-old woman was admitted for glandular abnormality on cervical smear and episodes of vaginal spotting. Two years before she had undergone an artificial abortion and has been using oral contraceptives since. Cytologically, the smear showed cohesive or loose clusters of monomorpheous, small glandular cells, forming

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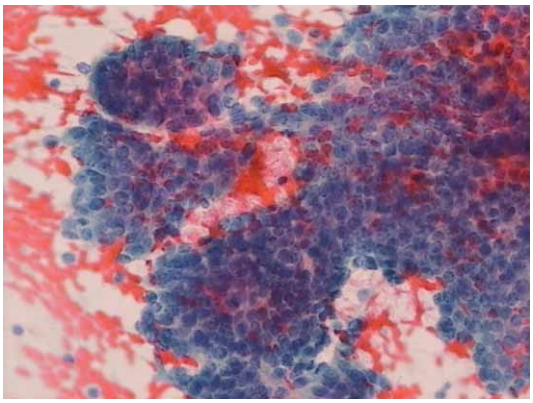

Fig. 1. Cervical cytology smear of villoglandular papillary adenocarcinoma showing clusters of cells forming papillary projections and branching epithelial sheets in a bloody background (Papanicolaou stain, ×200).

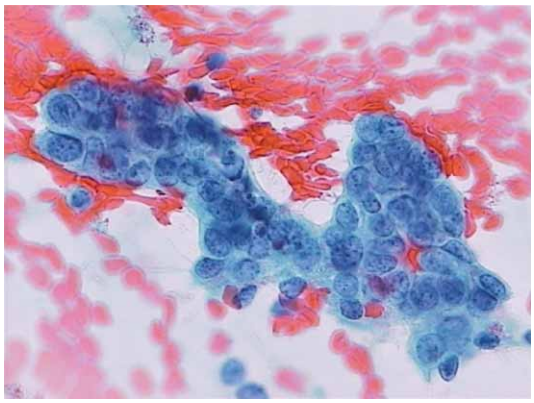

Fig. 2. Papillary fragment showing nuclear crowding and overlapping of atypical glandular cells with well defined, intact cytoplasmatic borders (Papanicolaou stain, ×400).

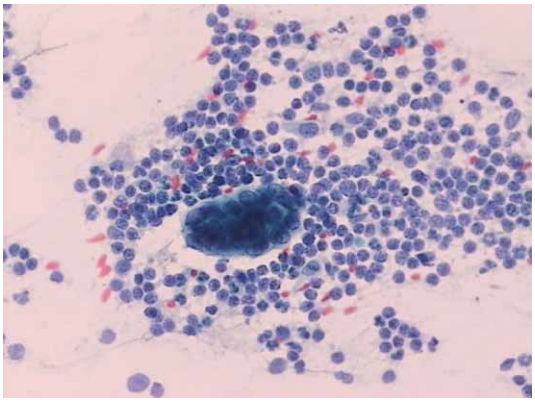

Fig. 3. Lymph node metastasis – three-dimensional ball-like cluster of cells of villoglandular papillary adenocarcinoma (Papanicolaou stain, ×200).

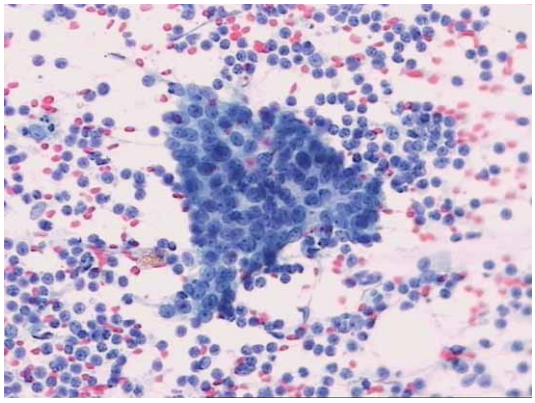

Fig. 4. Cytologic details of villoglandular papillary adenocarcinoma in lymph node metastasis showing slight feathering of the nuclei along the periphery, uniform, small, normochromatic to hyperchromatic nuclei with inconspicuous nucleoli (Papanicolaou stain, ×200).

papillary projections and branching sheets, with nuclear crowding and overlapping (Figure 1). The cytoplasmatic borders of the papillary structures were intact, yielding a smooth contour to the cell groups (Figure 2). Several dense, three-dimensional ball-like clusters of atypical glandular cells with well defined peripheral cytoplasmatic contour were also noted. Slight feathering of the nuclei along the periphery was noticed in just a few clusters, the nuclei were normochromatic to hyperchromatic, round to oval-shaped with minimal anisonucleosis and incospicous or absent nucleoli. Dispersed single atypical cells in the background were infrequently seen, while scattered apoptotic cells and mitoses could be observed. The background was bloody with an increased inflammatory exudate, but a tumor diathesis was absent. The cytological features were found out to be suspicious but not diagnostic of adenocarcinoma. Hence, they were reported as atypical glandular cells (AGC). The patient was immediately referred to colposcopy and histological confirmation. Gynecological examination revealed a hemorrhagic lesion originating from anterior and posterior lip of the cervix. Large loop excision of transformation zone (LLETZ) was performed. Histological examination confirmed VGA associated with lymphovascular space invasion. The patient underwent radical operative treatment (Piver type II). Intraoperative cytological examination of the lymph nodes revealed metastasis at right iliac and obturator lymph nodes. The cytological features in the lymph node metastases were the same as in the original tumor (Figures 3 and 4). After histerectomy the uterus specimen revealed a tumor mass measuring 1.5×1.3 cm in diameter. Histologically, cervical tumor was composed of papillary structures arranged in complex branching pattern (Figure 5). The morphology was typical for a well differentiated villoglandular adenocarcinoma. However, at its invasive edge foci of poorly differentiated carcinoma were observed. Vascular and lymphatic space invasion was prominent. The patient was diagnosed as having FIGO stage III B cervical cancer and underwent three cycles of chemotherapy (cisplatin, ifosfamide, mesna). Three months after surgery the patient was admitted for a sudden onset of urinary incontinence and fever. Abdominal CT (computerized tomography) scan revealed an enlargement of lymph nodes involving the distal part

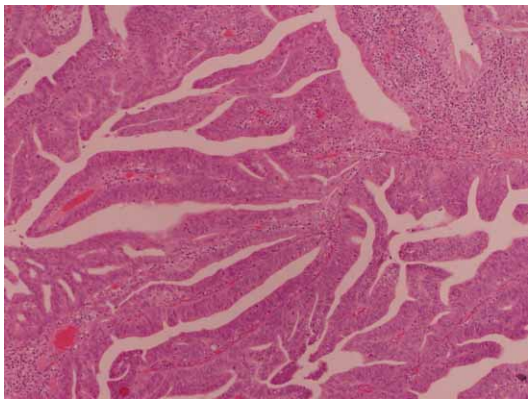

Fig. 5. Appearance of the papillae in villoglandular papillary adenocarcinoma of the uterine cervix (H & E stain, ×100).

of abdominal aorta and left kidney hilar nodes. A second laparotomy with paraaortal lymph node resection and removal of ureteral obstruction was performed. Microscopic examination confirmed multiple abdominal lymph nodes metastases. The patient received another three cycles of chemotherapy (cisplatin, paclitaxel) and radiotherapy of the pelvis. A PET/CT (positron emission tomography) scan detected widespread metastases to mediastinal lymph nodes and lungs. The patient was planned for an additional chemotherapy cycle, but she deceased of tumoral complications in the second year since the diagnosis was established.

Discussion and Conclusion

Villoglandular papillary adenocarcinoma is a distinct entity and rare histological variant of cervical adenocarcinoma, which is believed to have a favourable prognosis and predominantly develops in young women[4]. These tumors are often only superficially invasive and rarely exhibit lymphovascular invasion, leading some surgeons to conduct less radical surgeries[7]. However, a review of the literature reveals several cases with lymphovascular space involvement associated with lymph node metastases and disease spread[6,8]. Young and Clement suggested that VGA diagnosis should be reserved only for those lesions that are well differentiated, exclusively or almost exclusively composed of villoglandular papillary architecture, without an underlying component[4]. In our case foci of poorly differentiated carcinoma were found and this could be the reason of aggressive clinical course. Various authors have observed the association of other histological types of tumor in VGA that may contribute to disease progression such as squamous cell carcinoma[8,9] and adenocarcinoma *in situ*[10]. Therefore, a thorough search for coexistence of other type of malignant component is indispensable. Furthermore, diagnosing the disease at an inadequate material is not recommendable, since it may lead to undertreatment of a potentially fatal lesion[4].

The etiology of VGA of the cervix is still not well established. Oral contraceptives are thought to be involved in the pathogenesis of VGA. A previous research demonstrated a statistically significant difference in the incidence of VGA appearance and oral contraceptive use[11]. Other authors confirm that behavioral cofactors, such as oral contraceptive use and smoking can be excluded as risk factors[12]. This case confirms an association between VGA and taking oral contraceptives, since the patient had a history of hormone use. Although evidence of HPV infection generally is limited to squamous epithelium, numerous data support the extremely high frequency of HPV infection in invasive adenocarcinoma. A molecular study by polymerase chain reaction amplification of tumor DNA revealed a strong positive signal for HPV-DNA in VGA[12] and several other studies have reported that infection with HPV has an influence on the prognosis[12,13].

Abnormal cervical cytology in routine cervical screening could be the first sign of disease and lead to an early diagnosis of VGA. The major cytomorphological findings to be considered in the diagnosis of VGA are hypercellularity of the endocervical component, large flat sheets of cells showing nuclear crowding, overlapping and presence of papillary clusters[14]. Architecturally, elongated papillae and branching epithelial sheets in VGA display smooth cytoplasmatic borders and lack of feathery edge. Cytologically, the tumor cells have minimal nuclear pleomorphism and exhibit no more then moderate nuclear atypia[7]. Because of its rarity and subtle cytological changes, certain cases of VGA may be overlooked or misinterpreted as benign lesion. Papillary groups similar to VGA may be seen in chronic endocervicitis and microglandular hyperplasia, although in the latter case the cells are less atypical than those in VGA. Beside the benign lesions, the cytologic differential diagnosis of VGA includes malignant entities. When sheets of epithelial cells with a high nuclear-cytoplasmatic ratio are present, it may be difficult to differentiate VGA from carcinoma *in situ* involving the endocervical glands. In such cases the presence of papillary structures and less nuclear hyperchromasia may facilitate the diagnosis of VGA. Large, crowded epithelial sheets of adenocarcinoma *in situ* can be differentiated from VGA by its feathery edges, elongated hyperhromatic nuclei with prominent nucleoli and lack of papillary structures[7,15]. The distinction of VGA from other subtypes of adenocarcinoma, like papillary serous and clear cell adenocarcinoma, may not be difficult since these tumors show a greater degree of nuclear atypia and complex papillae[15].

Although recognition of the above morphological characteristics should facilitate the detection of VGA, the diagnosis of this entity on cervical smears is often difficult due to its relatively bland cytological features[16]. In the presented case the tumor cells and clusters showed only mild abnormalities and were recognized as being atypical, but the highest grade that could be assigned to the abnormal endocervical cells was AGC. Only with careful retrospective study it was possible to observe the specific cytologic features of VGA. It is doubtful whether these features would be detected by routine prospective screening. However, the most important role of cytologist in

such cases is to immediately refer the patient to colposcopical exam and histological diagnostic procedure.

The presentation of this case and evidence of similar cases suggest a need to further investigate the pathogenesis of the tumour and to identify potential risk factors that may influence the prognosis of a patient. Current literature is not entirely consistent in the definition of VGA or in the cytological features which suggest that a review of similar cases is needed. We hope that our presentation would assist in the future analyses and in the following investigation of this clinicopathologic entity.

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VILOGLANDULARNI PAPILARNI ADENOCARCINOM CERVIKSA S AGRESIVNIM KLINIČKIM TIJEKOM – PRIKAZ SLUČAJA

SAŽETAK

Viloglandularni papilarni adenokarcinom cerviksa (VGA) je rijedak, ali jasno definiran histološki podtip cervikalnog adenokarcinoma koji se najčešće pojavljuje u mlađih žena. Brojni prethodno opisani slučajevi s povoljnim kliničkim ishodom upućuju da je VGA indolentan tumor s vrlo dobrom prognozom. U radu prikazujemo slučaj dvadestdvogodišnje pacijentice koja je hospitalizirana zbog abnormalnog citološkog nalaza i povremenog pojavljivanja sukrvavog iscjetka. U Papa razmazu citološke promjene su bile suspektne, ali ne i dovoljne za potvrdu adenokarcinoma, te su stoga označene kao atipične glandularne stanice (AGC). Patohistološka analiza potvrdila je viloglandularni papilarni adenocarcinom cerviksa uz prisutnost limfovaskularne invazije. Pacijentica je podvrgnuta radikalnom operativnom zahvatu. Intraoperativna citološka analiza dokazala je prisutnost metastaza u limfnim čvorovima zdjelice. Utvrđeno je da se bolesnica nalazi u uznapredovalom stadiju bolesti – III B (FIGO). Tijekom dvogodišnjeg praćenja nastupila je progresivna diseminacija tumora koje je rezultirala smrtnim ishodom. Iako se smatra da VGA ima povoljnu prognozu, opisani su prethodni slučajevi sa zahvaćanjem limfnih čvorova. Citološka detekcija može uvelike pridonijeti ranom otkrivanju tumora, ali je često otežana. Potrebna su dodatna istraživanja patogeneze, dijagnostike i terapije ovog tumora.