

# Verrucous carcinoma of the cervix - diagnostic and therapeutic difficulties with regards to HPV status.

## Case report

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### Summary

Verrucous carcinoma of the cervix is of special interest because of its rare occurrence and frequently existing difficulties in the differential diagnosis, which in verrucous disease eventually leads to a final, more favorable diagnosis. We present a case report of cervical verrucous carcinoma as a rare variant of squamous cell carcinoma in a 65-year-old woman who underwent total hysterectomy based on initial histological diagnosis of cervical dysplasia. Special attention is focused on clinical assessment of the lesion with the depicted restriction of exfoliated cytology as well as misdiagnoses of inappropriately taken, even colposcopically directed biopsy, not covering a full thickness of biopsied tissue. The macro- and micromorphologic similarities of cervical verrucous carcinoma with condylomata acuminata on one hand and invasive squamous cell carcinoma on the other, inclined us to search for a common factor causing human papillomavirus infection.

*Key words:* Verrucous carcinoma; Cervical cancer; HPV.

### Introduction

The most frequent localization and first described case of verrucous carcinoma was of the oral cavity [1]. Less frequently this carcinoma occurs in the upper respiratory tract, occasionally in the anogenital region, including the vulva and vagina, and very rarely in the urinary tract or as a cervical lesion [2]. Verrucous carcinoma is a peculiar form of well-differentiated squamous cell carcinoma with a noninvasive biological behavior, slow, scanty symptomatic course and minimal, limited, local infiltrative growth modality, presenting macroscopically as thick, whitish exophytic layers of cauliflower-like, well-circumscribed masses. These columns of hyperproliferating squamous epithelium are easy to detach exposing the underlying stroma causing contact bleeding, resembling and suggestive of invasive cervical cancer. The histological view under microscopic examination shows a benign appearance with no or minimal atypia, nucleolar "silence" and rarely findings of mitotic figures. This biological characterization corresponds with a slow growing and locally recurrent rather than metastasizing cervical lesion of verrucous carcinoma [3].

Nevertheless the first case of cervical verrucous carcinoma was reported by Degefu *et al.* 30 years ago, and while its definition seems to be clear and legible, the diagnosis of verrucous cervical lesions is still difficult [4]. Simultaneously held investigations searching for an oncogenic factor in carcinogenesis within the cervical epithelium are concentrated on the HPV family. As it probably takes place in squamous cell carcinoma of the cervix, there is evidence of an etiologic association between HPV infection and verrucous differentiation of cervical lesions [5].

The process of diagnosis followed by therapy of cervical verrucous carcinoma is referred in this communication with special regard to any HPV types presented within the cervical lesion.

### Case Report

#### *Clinical data*

A caucasian patient, 65 years of age (gravida 1, para 1), presented with whitish, thick, irregular, epithelium visible in the vaginal speculum examination as a broad, lofty, white area resembling a leukoplakia, warty lesion covering the ectocervical area and spreading down through vaults on the vaginal walls as well as into the cervical canal, almost completely obstructing it. The patient's main complaint was vaginal discharge with itching and sometimes delicate dysuria. She presented with charts of four years of diagnostic and therapeutic procedures from elsewhere focused mainly at first on suspected uterine bleeding and afterwards on a cervical lesion and recurrent vaginal discharge and inflammation. The first admission was in May 1999 because of suspected, occasional postmenopausal bleeding when uterine D&C was performed. Histological examination showed paraepidermal epithelial and inflammatory cells with no diagnostic significance in very scanty tissue material. There were no abnormalities either at clinical examination or in biochemical tests, thus conservative treatment was initiated. There was no evidence of any abnormality on the cervix with a normal cervical smear result, classified as group 2 according to Papanicolaou. During the next three years the patient was treated several times because of vaginal inflammation which was also confirmed in cervical smears presenting normal and hyperkeratotic cells with acanthosis and severe inflammation, but with no evidence of a neoplastic process. The patient was treated locally with administered antibiotics, and estrogen supplementation was proposed. Afterwards, with no significant improvement and evidence of leukoplakia within the cervical lesion and hyper-dyskeratotic and inflammatory abnormalities

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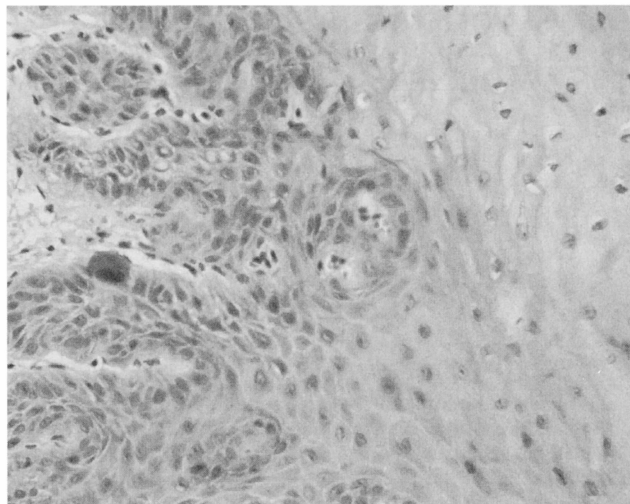
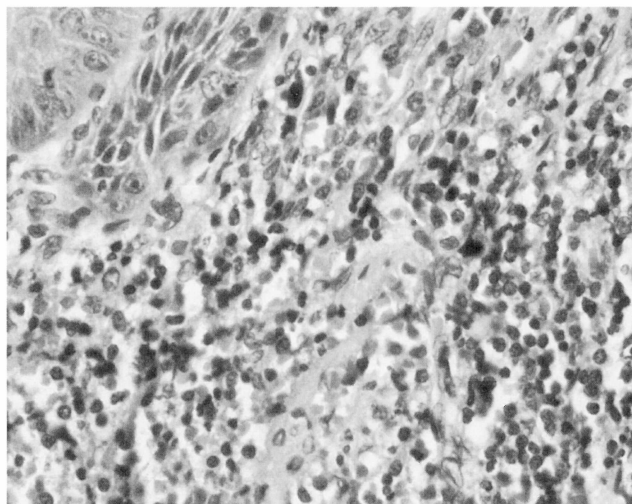


Figure 1. — Histological section of verrucous carcinoma – well-differentiated cells with few mitotic figures (magnification 400x).  
 Figure 2. — Histological section showing chronic deep inflammation and benign hyperplasia of the squamous epithelium (magnification 200x).

in the pap test with a suspicion of cervical blastoma, the patient underwent punch biopsy. Histological examination of the cervical biopsy revealed fragments of squamous epithelium with traits of parakeratosis and dyskeratosis in scanty tissue. Material from the endocervical canal abrasion was described as completely unsuitable for diagnosis with the suggestion to repeat the diagnostic procedure. Punch biopsy was performed the following month with the results showing a glandular cervical lesion in the epidermidalization stage with focal middle dysplasia on histological examination.

After five months the patient presented at our hospital, and based on histological diagnosis and clinical overview as mentioned above, she underwent total abdominal hysterectomy with bilateral ovariectomy. Taking into account that abnormal epithelium was observed within one-third of the upper part of the vaginal wall, that tissue fragment was excised as well. There was no clinical evidence that the parametrium or local lymph nodes were involved in the process. Final histological examination confirmed a verrucous type of cervical cancer. Post surgical recovery was normal and the patient was discharged from hospital on the tenth day.

### Materials and Methods

A cervical smear for HPV detection was taken prior to treatment. Genomic DNA was extracted from the swab using Genomic Prep Plus (A&A Biotechnology) according to the manufacturer's instructions. The presence of HPV DNA was detected by the PCR method using primers: pU-1M/pU-2R (high risk) and pU-31B/pU-2R (low risk) described elsewhere [6]. All PCR reactions were performed using MJ Research Thermal Cycler (Model PTC-200, Watertown, MA, USA). PCR was carried out in a total reaction volume of 25  $\mu$ l; the reaction mixture contained 2.5  $\mu$ l 10-fold PCR buffer, 5  $\mu$ l DNA, 40  $\mu$ M of each dNTP (Promega), 1U of HotStarTaqDNA polymerase (Qiagen GmbH, Hilden, Germany) and 200 nM of each primer.

PCR was carried out under the following conditions: 15 minutes at 94°C in order to activate HotStarTaq DNA Polymerase, 1 min denaturation at 94°C, 1 min annealing at 55°C, 1 min extension at 72°C for 30 cycles, with an additional 5 min

extension for the last cycle. Controls with water replacing templates were included in all experiments. The amplification product was detected on 2% agarose gel. Ethidium bromide-stained gels were visualized under UV illumination.

Material for histological examination was formalin-fixed and paraffin-embedded. Histological and cytological slides were stained with hematoxylin and eosin.

### Results

Histological examination revealed verrucous carcinoma, a well-differentiated type of squamous cell cervical cancer, infiltrating the entire endocervix (Figure 1). The neoplastic process spread superficially up to the internal cervical os. There was no involvement of the endometrium where atrophy and an endometrial polyp were found. The majority of the tumor mass with mainly exophytic, regular, papillary, with a pushing growth pattern extended to the vaults and walls of the vagina. Chronic, deep inflammation and benign hyperplasia of squamous epithelium with parakeratosis within the vaginal walls was also confirmed on histologic specimens (Figure 2). No other significant abnormalities in spite of salpingitis and fibrosis were histopathologically revealed. The papillary mass consisted of well-differentiated neoplastic cells of squamous origin with a clear benign appearance. Distinct acanthosis with strongly marked hyperkeratosis and parakeratosis was observed. The cells were normal in size with centrally located, "silent" nuclei, and very few mitotic figures were visible. Koilocytes were noted occasionally both in the cervical smear and histological preparation. An inflammatory reaction was strongly depicted in the surrounding tissue which also involved stroma.

PCR analysis for human papilloma virus performed on the cervical smear showed presence of HPV type 16.

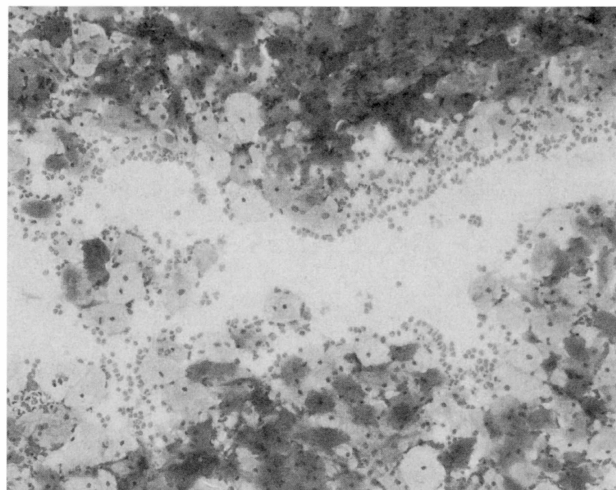


Figure 3. — Exfoliated cytology showing acanthosis and dyskeratosis (H&E).

### Discussion

The most frequent localization of verrucous carcinoma within the female genital tract is the vulva [2]. This rare neoplastic disease concerns mainly elderly, postmenopausal women and is accompanied by dystrophic changes with senile mucous atrophy [4].

The diagnosis of verrucous carcinoma is usually difficult and the differential diagnosis, especially excluding well-differentiated invasive squamous cell carcinoma, is even more complicated. It is usually based on various stages of cellular atypia and infiltration of underlying stroma. The clinical resemblance to condylomata acuminata could cause some problems in the differential diagnosis, but multiple, small, warty lesions with fibrovascular cores form it. All mentioned diseases are probably related to HPV infection, thus macro- and microscopic confirmed findings, like koilocytosis or papillary structures, have little diagnostic value. Nevertheless, because of the distinct biological and clinical behavior of verrucous carcinoma, it is very important to make a proper, final diagnosis [7]. These diagnostic efforts find their therapeutic reasoning in less radical treatments compared to invasive cervical cancer, with usually local excision procedures. Verrucous carcinoma has very limited invasive potential with no lymph node metastasis giving a better prognosis with no need for exploration. In face of the evidence that postoperative radiation therapy may transform verrucous carcinoma into an aggressive, neoplastic process with metastatic potential, histologic knowledge of tumor type is crucial for further medical procedures. On the other hand, it must be depicted that inadequate excision is followed by local recurrence of the lesion [2].

Our own experience confirms that exfoliated cytology is not generally helpful in the diagnostic process where we usually find groups of normal epithelial cells as well as abundant acanthotic and hyperkeratotic cells with a severe inflammatory smear background (Figure 3). As

described by others [3], distinguishing the morphological peculiarity of dyskeratotic cells seems to have little value, mainly because of its low specificity. Another problem in the described case is that microscopic examination of biopsied cervical tissue may not provide a correct diagnosis, if any. A pivotal factor is to take the full thickness of the lesion for a correct diagnosis of verrucous carcinoma as described by others [8]. A superficial and small biopsy giving inadequate tissue material may lead to misdiagnosis, and what is worse, to omission of focal invasive squamous cell carcinoma. In our case cervical smears did not show the characteristic abnormalities with any suggestions of verrucous carcinoma. Histological examination was worthless at the first procedure and only confirmed a dysplastic process in the second. Clinical examination provided an argument for hysterectomy over conization, and postoperative histologic examination indicated a final diagnosis of verrucous cervical cancer.

A strong relation between cervical dysplasia or cancer and HPV infection was firmly determined. There is also some evidence of HPV presence in verrucous carcinoma but generally in vulvar and vaginal lesions, and mostly HPV type 6/11 [9]. It is interesting that absence of oncogenic high-risk HPV types may lead to biological behavior of uncommon metastasizing verrucous carcinoma with slow, superficial growth and lack of infiltration of the underlying stroma. Conversely, the presence of oncogenic HPV types could indicate a more aggressive growth pattern and a worse prognosis caused by tumor recurrence even after radical excision. According to accessible data, local recurrence is seen in almost 50% of women – probably due to incomplete excision or ineffective radiotherapy [2]. In most opinions, radiotherapy itself may lead to anaplastic transformation of verrucous carcinoma into an invasive squamous epithelial cervical cancer. There are also unique data confirming different beneficial effects of such additional treatment [10].

### Conclusion

Verrucous carcinoma of the uterine cervix is not only a special histologic type but also requires special attention during diagnostic and therapeutic procedures. Consequently close collaboration between the clinician, cytologist and pathologist is crucial for eventual medical procedures. Clinical information and macroscopic growth patterns, usually with no need for colposcopic examination, may lead to a proper biopsy procedure, which in this case could be diagnostic conization to provide sufficient tissue for careful histopathologic examination. Accurate diagnosis based on histomorphology within the whole lesion allows the clinician to perform total excision of the tumor mass and postoperative histological verification with no need for additional radiotherapy. It is obvious that close follow-up of the patient afterwards with gynecological, cytological and colposcopic examination is required.

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