CASE REPORT

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Verrucous Carcinoma of the Uterine Cervix Arising in a Giant Condyloma Acuminatum, Associated with Ichthyosis of the Endometrial Cavity

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ABSTRACT We describe a unique presentation of a cervical verrucous carcinoma (VC) associated with ichthyosis of the uterine cavity in an 80-year old woman. Areas of transition from a giant condyloma (GC) were present in the VC. This paper also includes a review of the relevant literature. VC of the cervix is an uncommon malignancy, and transition of a GC to VC is an interesting finding, confuting the theory that they represent distinct entities, with different risk factors. Differently from GC, VC is considered to be causally related to HPV in a minority of instances. Our results of p16 immunohistochemistry, the surrogate marker of high-risk human papillomavirus (HPV) infection, appear to speak against the causal role of HPV in the pathogenesis of VC. Ichthyosis uteri may occasionally be associated with a cervical or endometrial malignancy; however, we are not aware of any patient showing VC, GC and ichthyosis uteri at the same time.

Keywords: Verrucous carcinoma; giant condyloma; human papillomavirus; squamous cell carcinoma; uterine cervix

Squamous cell carcinomas (SCC) of the female genital tract are classified microscopically by the World Health Organization as keratinising, non-keratinising, basaloid, verrucous, warty, papillary, lymphoepithelial-like, squamotransitional, and spindled/sarcomatoid variants.[1] Most of them are characterised by a high-grade neoplastic epithelium with infiltrative stromal invasion**.** When they affect the cervix, they may spread into the myometrium or the vagina.

Verrucous carcinoma (VC) is an uncommon exophytic, slowly enlarging, well-differentiated variant of low-grade SCC. It is characterized by dense superficial keratinisation, dyskeratosis, minimal cytological atypia, rare mitoses, mild to absent koilocytosis and bulbous, pushing, stromal invaginations or puzzle-like nests in the stroma, rather than infiltrating borders.

VC in genital regions is considered, histologically, to be in the spectrum of giant condyloma (GC), the latter being an exuberant growth of condyloma acuminatum. GC appears to be a sexually transmitted disease, as viral cytopathic changes and low-risk human papillomavirus (HPV) types 6 and 11 are consistently identified. Association with HPV is less consistent in VC.[2,3] We describe a GC of the cervix with transition into VC and concomitant ichthyosis of the endometrium.

CASE REPORT

A 80-year-old woman presented with metrorrhagia of several months duration. Gynecologic examination revealed a diffuse whitish thickening of the cervical mucosa. Two repeat cervical biopsies demonstrated only anucleated squames. Transvaginal ultrasound revealed in addition a vascularized intracavitary, placoid, uterine neoplasm and positron emission tomography scan showed a 13.7 mm area of hypercaptation in the cervix (SUV_{max} 5.6). Magnetic resonance imaging failed to detect any lym-

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phadenopathies. A Wertheim hysterectomy and pelvic node dissection were carried out without complications, and the postoperative course was uneventful.

On gross examination, the uterus measured 9x4x3.3 cm. The cervix and the endometrial cavity were completely replaced by a white circumferential growth, of hard consistency and a corrugated appearance (Figure 1). Histologically, the distal cervix showed an exophytic lesion with an undulating, thick hyperkeratotic squamous surface, composed of pointed papillary projections with a fibrovascular core. Limited areas of koilocytic changes were noticed, as well as a flat, noninvasive epithelial-stromal interface (Figure 2a). The giant condyloma-like area abruptly confined with normal mucosa at the vaginal fornix, whereas in the remaining endocervix, an exo-endophitic growth of squamous cells showing mild cytological atypia was observed. These tumour cells displayed minimal loss of polarity, few mitoses and no koilocytotic changes. Stromal invasion displayed a characteristic pushing border (Figure 2b). Tumour cells were only focally immunoreactive for p16 and the strongest reaction was found in the basal and parabasal cells. p53 and Ki67 nuclear positivity was localised to the basal layer of the neoplastic squamous epithelium. Immunostains for HPV failed to detect viral infection. The endometrial mucosa was entirely replaced by benign squamous epithelium with hyperkeratosis and parakeratosis (Figure 3a). Occasional residual basalis gland and stroma could be appreciated, with initial foci of squamous metaplasia of the endometrial glands (Figure 3b). The fallopian tubes and ovaries were atrophic, without neoplastic infiltration. Parametrial tissue and regional lymph nodes were also negative. The diagnosis was VC of the uterine cervix associated with a GC and ichthyosis uteri. Informed consent for publication was received from the patient.

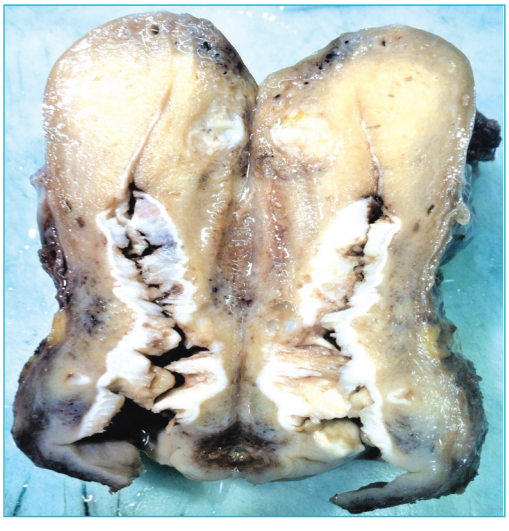

FIGURE 1: Intrauterine surface spread of cervical VC visually reminding a "cake icing."
VC: Verrucous carcinoma.

DISCUSSION

The present case showed several peculiar characteristics. Firstly, VC of the female genital tract is an uncommon (about 1-2% of all gynecological cancers) and a still poorly understood entity. To date, <50 cases have been reported in the English literature, only a minority of them involving the cervix.[3] As in our patient, it usually affects postmenopausal patients

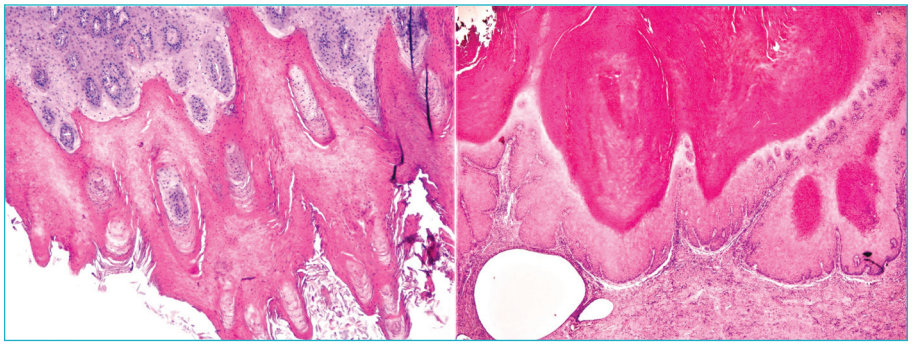

FIGURE 2: a) Giant condyloma of the uterine cervix is a large, warty lesion showing distinct fibrovascular cores. b) Verrucous carcinoma of the cervix, showing bland epithelium and blunt pattern of cervical stroma invasion (H&E, 20 x, respectively).

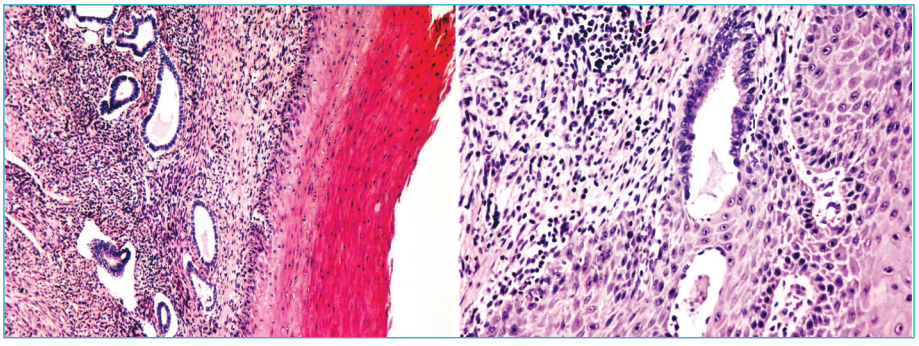

FIGURE 3: **a)** Replacement of the endometrial surface by benign stratified squamous epithelium, showing focal parakeratosis. **b)** The mature squamous epithelium extends into the glandular lumens (H&E, 100X, and 200 X, respectively).

in the seventh-eighth decades, presenting as a slow-growing bulky, fungating mass that shows a high recurrence rate and, an exceedingly low incidence of metastasis.

Also GC is an uncommon entity (0.1% in the general population), usually occurring in the vulva, anus, perineum, or penis, and only exceptionally affecting the uterine cervix or the endometrium.[4] Differently from VC, it presents in young patients and is associated with impaired immunity (human immunodeficiency virus-related, chemotherapy with immunosuppression, diabetes, alcoholism) or pregnancy. Microscopically, it displays a papillary architecture with finger-like projections containing a fibrovascular core and a flat, noninvasive epithelial-stromal interface. The age of our patient did not match the mean age for GC, and it is possible that cervical cases are less aggressive than vulvar or anal GC, so as to remain hidden and undiagnosed for several years, until advanced age or malignant degeneration.

Transition of GC to VC, is another interesting finding in the present case, confuting the theory that they represent distinct entities, with different risk factors.

There are other instances of VC arising in GC in the literature, mainly in non-cervical sites. In the case reported by Ahsaini et al, the malignant verrucous component arose from a GC of the external genitalia and perianal region in a 54 year-old Moroccan man, after 10 years of neglect.[4] The advanced age of our patient also points to a longstanding condylomatous disease. However, the malignancy mostly associated with GC is SCC, and not VC. It can be considered that GC represents an intermediate lesion between condyloma acuminatum and either VC, or SCC. On the other hand, also VC may transform, with time, into a SCC.[5] Some authors believe that VC and GC are a spectrum of the same process mainly due to the overlapping histological features. However, GC is associated with low-risk HPV genotypes, with absent or weak p16 expression by immunohistochemistry, whereas tissue samples of VC are in most cases devoid of HPV. However, low-risk (types 11 and 53) or high-risk (type 16) genotypes of HPV were detected in 25% of reported cervical VC, showing at any rate that such association is possible.[6] Why should HPV infection disappear in the GC-associated VC eludes us. An explanation could be that the methods used for HPV detection were suboptimal, or that only a subset of high- and low-risk mucosal HPV types was investigated. Otherwise, low-risk HPV types may initiate the growth process and the chronic epithelial irritation could subsequently contribute to the development of a malignant phenotype.

Our results of p16, the surrogate marker of high-risk HPV infection and HPV immunohistochemistry appear to speak against the causal role of HPV in the pathogenesis of VC, as the expression of p16 was weak, cytoplasmic and focal in the tumour cells.

Focally invasive SCC of usual type is detected in approximately 30-56% of non-cervical VC cases.[4,7] Average time for malignant transformation is known to be approximately 5 years.[8] Although stromal invasion can be very focal, VC with destructive stromal invasion should be classified as invasive SCC.[9] In the

present case, we failed to find focally invasive SCC of usual type.

The third interesting feature in our case is the diffuse replacement of the endometrial cavity by a mature squamous epithelium. There are other published instances of ichthyosis uteri associated with a cervical or endometrial malignancy, and other cases that were labelled as ichthyosis, but showed extension of a cervical neoplasia in the endometrial cavity.[10-13] This pattern of endometrial spread was occasionally seen with GC as well.[14] VC lacks pathogenic p53 mutations and shows low mitotic index.[15] Accordingly, our case showed positive results for p53 and ki67 only in the epithelial basal layer.

VC of the uterine cervix is a rare histologic subtype of SCC, which can occasionally be associated with ichthyosis uteri. VC can arise from GC, and the latter develops from ordinary condylomata, as a result of the combination effect of immunosuppression and carcinogenic factors. As the incidence of condyloma is steadily increasing in the non-industrialized nations, we may expect in the future the occurrence of more GC/VC in the female genital tract.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Irene Pecorella;* ***Design:*** *Giorgio Maria Masci;* ***Control/Supervision:*** *Irene Pecorella;* ***Data Collection and/or Processing:*** *Hiba Wazeer Alzoubi;* ***Analysis and/or Interpretation:*** *Hiba Wazeer Alzoubi;* ***Literature Review:*** *Giorgio Maria Masci;* ***Writing the Article:*** *Emma Rullo;* ***Critical Review:*** *Irene Pecorella.*

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