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Warty carcinoma of uterine cervix - review of the literature and case report

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ABSTRACT

Introduction. The Histological Classification of Epithelial Tumors of the Uterine Cervix of the World Health Organization includes inter alia warty carcinoma as a variant of squamous cell carcinoma. Until now several case reports and studies have shown that this particular cancer is associated with human papillomavirus/ HPV infection.
Case presentation. A 58-year-old woman presented with a vegetant cervical tumour. Biopsy samples were collected from the tumour, and the histological exam successively confirmed the warty cell carcinoma. Additional tests revealed the presence of single human papillomavirus/ type-45. An immunohistochemistry exam was performed in order to confirm the diagnosis, and also to highlight the relationship between the potential causal factors and the morphological appearance. This allowed the confirmation of the diagnosis, and added new elements able to define the characteristics of this form of cancer. The treatment included radiotherapy and radical hysterectomy with anexectomy, and pelvic lymphadenectomy. The evolution was favorable, with no signs of local recurrence or metastasis in the past five years.
Conclusions. Warty carcinoma, relatively similar to condyloma acuminatum or verrucous carcinomas, has specific immune-histochemical features that differentiate it from other variants of squamous cell carcinoma. The HPV genotype 45 can be considered a causative factor in the pathogenesis of cervical warty carcinoma. Even so, warty carcinoma appears not to be caused by a specific HPV subtype (or a combination of several specific genotypes), being rather a multifactorial affection.

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Introduction

The Histological Classification of Epithelial Tumors of the Uterine Cervix by the World Health Organization (WHO) considers warty carcinoma as a variant of squamous cell carcinoma. Warty (condylomatous, verruciform) carcinoma was first described in 1982 by Ratskar et al., studying at that time a number of cases of vulvar carcinomas [1]. Specifically, it has an exophytic appearance very similar to condyloma acuminatum or verrucous carcinoma. Ratskar and colleagues identified several specific histological features, and Kurman notes that this disease has a particular clinical behavior that would be intermediate between verrucous and well-differentiated squamos cell carcinomas [1, 2]. Verrucous carcinoma is considered a gentle form that typically remains local and almost never metastasizes; in contrast, warty carcinoma seems to have a more aggressive behaviour, lymph node metastases being documented by Kurman et al. in 1993 [2].

Accurate diagnosis is important, as undesirable confounding with condyloma acuminatum and worm carcinomas can have major medical implications. According to current concepts, treatment for the warty carcinoma should be the same as the standard treatment accepted for typical squamous carcinomas [2]. Cervical cancer is often associated with infection by the human papillomavirus (HPV), which is considered an important (but not necessary) factor for its occurrence [3-5]. Until now, the genotypes identified in cases of warty carcinoma were represented by type: 6, 11, 16, 18, and 33. Several researchers, finding multiple HPV types (6, 11, 16, and 33) in the same lesion, stated that multiple-virus

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infections would be required/ characteristic for the warty carcinoma occurrence [6-8].

Due its rarity, so far only isolated cases or limited series have been studied and reported. The answer to the question 'What factors lead to this particular form of cancer' is still unknown, being perhaps a multifactorial disease.

Case presentation

This paper describes the case of a 58-year-old woman. Medical history details of the case revealed that the patient had one birth, no abortions, and one ectopic tubal pregnancy at the age of 26. The menopause occurred at the age of 43. Cigarette consumption averaged 20 per day. In the last 10 years, the patient has not had a medical examination, for either preventive or diagnostic purposes.

The patient presented to the gynecologist for vaginal bleeding, which appeared occasionally in the preceding two months, in association with pain in the lower abdomen. An exophytic cervical tumor (approx. 6 cm in diameter) was found upon gynecological exam, which showed ulcerous and hemorrhagic areas bleeding easily when touched. The left parameter was infiltrated in the juxta-uterine half. It was established that biopsy was necessary, so multiple samples were collected from the lesion. Histological examination of the biopsy revealed a tumoral proliferation with the aspect of an invasive squamous carcinoma, and numerous intratumoral cells with koilocytic atypia, which are considered characteristics of warty cell carcinoma. Additional tests were performed for determining the presence of HPV infection. The tests allow the individual qualitative detection (genotyping) of 37 types of HPV: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, IS39 and CP6108. The HPV-45 type was the only one detected.

In order to confirm the diagnosis and also to reveal the relationship between the potential causal factors and morphological appearance, an immunohistochemistry exam was performed. *CK34beta E 12* (CK903) was diffusely positive, *vimentin* (VIM) was negative in the tumor, *P16* was negative and *Ki67* was positive in 30% of the tumoral cells.

The pre-therapeutic computer tomographic scan did not identify any enlargement of the lymph nodes and confirmed the local extension of the disease. After FIGO classification, the disease was categorized as Stage II-B. The patient underwent radiotherapy followed by radical hysterectomy, as well as bilateral anexectomy and pelvic lymphadenectomy. After surgery, the patient had no major complications and was discharged 8 days after the intervention.

The histological exam of the surgically removed tissues did not reveal any remaining disease or node metastases. Evolution was favorable, with no signs of local recurrence or metastasis in the last five years since surgery was performed.

Discussion

Warty carcinoma is considered to be a rare variant of squamous cell carcinoma. It was first described by Ratskar et al. in 1982 with reference to the vulva, but it is possible that the carcinoma negosa also appears in other places, like the cervix, skin, anus and the buccal mucosa. Sometimes it can reach a considerable size. At the uterine cervix, warty carcinoma occurs mainly in women in the peri-menopausal and postmenopausal periods, while the vulvar involvement is mainly observed in younger women [1]. Ratskar also defined the classical features of warty carcinoma: the papillary architecture, the stromal invasion, and the koilocytic change with significant atypia [1, 9].

In a biopsy specimen (as in our case) it is often difficult to distinguish the warty (condylomatous) carcinoma from a condyloma acuminatum or a verrucous carcinoma. The invasion, characteristic for the warty carcinoma, usually measures only a few millimeters and is composed of invasive nests, as described by Ratskar [3, 10]. The distinction from a condyloma may be difficult when the invasive nests are not well developed, a situation in which the real nature of the lesion cannot be correctly established. The presence of significant atypia and of atypical mitoses in any condylom (that architecturally is typical) should raise the suspicion of warty carcinoma [2-4].

Verrucous carcinomas invade locally, rarely metastasize, and resemble the warty carcinomas because they are often exophytic and have frond-like papillae. However, in contrast with verrucous carcinoma, the warty carcinoma has atypical koilocytes present in the exophytic papillations and, as a sign of a more aggressive behaviour, lymph node metastases have been reported more frequently [2]. Furthermore, the invasion that is characteristic of warty carcinoma resembles the invasion of differentiated large cell carcinoma (with a diffusely or irregular edge) rather than the pushing edge of verrucous carcinoma [5].

Keratinization may be present in the invasive nests, but it is not surrounded by well-glycogenated cells as in the case of a verrucous carcinoma. Mitosis occurs at a larger scale compared to verrucous carcinoma, and is frequently atypical [1,2]. In addition, unlike the case of verrucous carcinoma, cervical intraepitelial neoplasia with warty and/or basaloid features is often present in the adjacent epithelium [2, 6].

CK34betaE12 is a specific antibody for high molecular weight cytokeratins (1, 5, 10, 14) that can be useful in separating benign from malignant proliferations [7-9]. In our case, CK34beta E 12 (CK903) was diffuse-positive in all samples.

Vimentin (VIM), a protein found in mesenchymal cells as a major cytoskeletal component, is used as a marker of mesenchymally-derived cells or cells undergoing an epithelial-to-mesenchymal transition. Usually it is used as

a sarcoma marker to identify the mesenchyme. As expected, VIM is negative in the warty carcinoma tumour.

P16 is a tumour suppressor gene product which is overexpressed in most cervical carcinomas and dysplasia, being associated with high-risk infection of human papilloma virus (HPV) [10-12]. For p16 compound, two patterns of positive staining were reported: "spotty" in which positive cells were scattered throughout the lesion, and "band" in which >90% of the positive cells were stained in a contiguous manner [13,14]. Spotty p16 immunoreactivity was rarely observed and was considered non-specific [15,16]. A band-like pattern of p16 immunoreactivity was seen in intraepithelial neoplasia cases and correlates with the presence of high-risk HPV infection [12, 14]. In the condyloma cases, the band of p16 positive staining was not reported [16, 17]. In our presented case, the *P16* was also negative.

Ki67 is a nuclear protein, many studies being performed in order to assess its role and expression in the neoplastic cells**.** It is considered useful in the diagnosis and grading of intra-epithelial lesions and cancers. More than 50% of nuclei stained positive for Ki67 in a significant proportion of CIN cases, but not in the normal tissue or condyloma cases.

Several studies show that high-grade CIN is strongly associated with a band-like pattern of p16 staining, and that the Ki67 positivity is encountered in >50% of the squamous cell nuclei. On the other hand, the absence of a p16 band of positivity coupled with Ki67 positivity in <50% of nuclei was frequently associated with benign lesions [12,14,15]. From this perspective, the results of our case that need emphasis are: p16 was negative and Ki67 positive in 30% of nuclei. The diagnosis was mainly based on histological appearance of stromal invasion and the presence of koilocyte cells with significant atypia.

The coexistence of HPV infection and women's genital squamous neoplasia has been studied extensively over the last decades. Human papillomaviruses are generally considered a necessary factor for the occurrence of cervical cancer [3, 18]. The association between warty carcinoma and the infection with human papillomaviruses has also been reported. According to literature data, warty carcinoma was most commonly found in association with genotypes 16 or 18. However Cho et al. reported concomitant infection with several subtypes of HPV (6, 11, 16, 33) in 6 cases of 9 warty carcinomas of the cervix studied, and stated that multiple-virus infection appears to be another characteristic of warty carcinoma [2-5, 8]. Generally, single/ low risk-HPV types are only rarely associated with high grade squamous intraepithelial lesions or cancer. There are possible exceptions: Padberg and colleagues reported a case of metastatic warty carcinoma of the cervix associated with a single/ low-risk HPV type 6 [6,7, 19].

In the present case, the human papillomavirus DNA typing revealed the presence of a single human papillomavirus, more precisely the type-45. HPV-45 papillomavirus is considered to belong to the high-risk HPV types. Nevertheless, it can also be encountered in benign lesions. After reviewing recent literature data, we found no other case in which the co-existence of HPV-45 and cervical warty carcinoma has been reported.

In addition to HPV infection, a number of additional factors seem to be involved in oncogenesis of the cervical cancer: other genital infections, local exposure to carcinogens, immune factors, *genetic or hormonal factors*, and smoking. The current literature does not contain sufficient evidence regarding the degree of involvement of all these cofactors.

The relationship between HPV infection and other coexisting risk factors on the one hand, and the histological morphology of the tumour on the other hand are unknown, but from our perspective it seems that the subtype 45 of HPV does not play a key role in this process.

Conclusions

Warty carcinoma may have some specific immune-histochemical features (useful to differentiate it from others variants of squamous cell carcinoma) but these features are not very consistent, so that the importance of a careful and detailed histological examination remains the basis of the diagnosis.

In the presented case, the human papillomavirus DNA typing revealed the presence of a single genotype of human papillomavirus, represented by the type 45, so that this element can be considered a possible causative factor in the pathogenesis of cervical warty carcinoma.

In other studies, warty carcinoma was detected in association with other subtypes of HPV; consequently, the appearance of this histological variant of squamous cell carcinoma does not seem to be caused by a specific HPV subtype. The complex relationship between HPV infection, coexisting risk factors, and morphological aspect should be further investigated.

Authors contributions

OGO has contributed to the acquisition, analysis and interpretation of data, conception and design of the article, as well to the drafting of the manuscript, CMP has contributed to the analysis and interpretation of data and participated in the drafting of the manuscript, revising it critically. All authors read and approved the final manuscript.

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Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient for the study and publication of this article. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

References

1. Neill SM, Lewis FM. Ridley's The Vulva (3rd edth). Cysts and neoplasms of the vulva, 2009; Wiley-Blackwell, pp. 181.
2. Kurman RJ, Toki T, Schiffman MH. Basaloid and warty carcinomas of the vulva. Distinctive types of squamous cell carcinoma frequently associated with human papillomaviruses. *Am J Surg Pathol.* 1993;17(2):133–145. doi:10.1097/00000478-199302000-00005
3. Insinga RP, Liaw KL, Johnson LG, Madeleine MM. A systematic review of the prevalence and attribution of human papillomavirus types among cervical, vaginal, and vulvar precancers and cancers in the United States. *Cancer Epidemiol Biomarkers Prev*. 2008;17(7):1611–1622. doi:10.1158/1055-9965.EPI-07-2922.
4. Muñoz N, Castellsagué X, de González AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. *Vaccine*. 2006; 24 Suppl 3: S3/1–S3/10. doi: 10.1016/j.vaccine.2006.05.115
5. Petry KU, Köchel H, Bode U, et al. Human papillomavirus is associated with the frequent detection of warty and basaloid high-grade neoplasia of the vulva and cervical neoplasia among immunocompromised women. *Gynecol Oncol*. 1996;60(1):30–34. doi:10.1006/gyno.1996.0007.
6. Padberg BC, Bode B, Zimmermann DR. Metastatic warty (condylomatous) carcinoma of the uterine cervix associated with low-risk HPV type 6. *Acta Cytol*. 2006;50(2):235–238.
7. Sams SB, Rosser JA. Metastatic Urothelial Carcinoma to the Uterine Cervix: A Case Report of a Rare Entity and Review of the Diagnostic Differential. *Int J Gynecol Pathol*. 2017; 36(5): 493–498. doi: 10.1097/PGP.0000000000000343.
8. Cho NH, Joo HJ, Ahn HJ, Jung WH, Lee KG. Detection of human papillomavirus in warty carcinoma of the uterine cervix: comparison of immunohistochemistry, in situ hybridization and in situ polymerase chain reaction methods. *Pathol Res Pract*. 1998;194(10):713–720. doi: 10.1016/S0344-0338(98)80131-3.
9. Rowland DL, Motofei IG, Popa F, Constantin VD, Vasilache A, Paunica I, Balalau C, Paunica GP, Banu P, Paunica S. The postfinasteride syndrome; an overview. *Journal of Mind and Medical Sciences* 2016; 3(2): 99-107.
10. Ng WK, Cheung LK, Li AS. Warty (condylomatous) carcinoma of the cervix. A review of 3 cases with emphasis on thin-layer cytology and molecular analysis for HPV. *Acta Cytol*. 2003;47(2):159–166. doi:10.1159/000326497.
11. Aroni K, Lazaris AC, Ioakim-Liossi A, Paraskevakou H, Davaris PS. Histological diagnosis of cutaneous "warty" carcinoma on a pre-existing HPV lesion. *Acta Derm Venereol*. 2000; 80(4): 294–296. doi: 10.1080/000155500750012216.
12. Cristian Bălălău, Stefan Voiculescu, Ion Motofei, Răzvan Valentin Scăunasu, Carolina Negrei. Low dose Tamoxifen as treatment of benign breast proliferative lesions. *Farmacia*. 2015, 63(3): 371- 375.
13. Moinfar F, Man YG, Lininger RA, Bodian C, Tavassoli FA. Use of keratin 35betaE12 as an adjunct in the diagnosis of mammary intraepithelial neoplasia-ductal type--benign and malignant intraductal proliferations. *Am J Surg Pathol*. 1999; 23(9): 1048–1058. doi:10.1097/00000478-199909000-00007.
14. Klaes R, Friedrich T, Spitkovsky D, et al. Overexpression of p16(INK4A) as a specific marker for dysplastic and neoplastic epithelial cells of the cervix uteri. *Int J Cancer*. 2001; 92(2): 276–284. doi: 10.1002/ijc.1174.
15. Dimcevici Poesina N, Bălălău C, Bârcă M, et al. Testicular histopathological changes following sodium fluoride administration in mice. *Rom J Morphol Embryol*. 2013;54(4):1019–1024.
16. Klaes R, Benner A, Friedrich T, et al. p16INK4a immunohistochemistry improves interobserver agreement in the diagnosis of cervical intraepithelial neoplasia. *Am J Surg Pathol*. 2002;26(11):1389–1399. doi:10.1097/00000478-200211000-00001
17. Balalau DO, Sima RM, Bacalbasa N, Banu P, Balalau C, Ples L, Stanescu AD. High-grade cervical dysplasia in pregnancy psychological and medical challenges. *Journal of Mind and Medical Sciences* 2017; 4(1): 24-30. doi: 10.22543/7674.41.P2430

18. Walts AE, Lechago J, Bose S. P16 and Ki67 immunostaining is a useful adjunct in the assessment of biopsies for HPV-associated anal intraepithelial neoplasia. *Am J Surg Pathol*. 2006;30(7):795–801. doi:10.1097/01.pas.0000208283.14044.a9

19. Conscience I, Jovenin N, Coissard C, et al. P16 is overexpressed in cutaneous carcinomas located on sun-exposed areas. *Eur J Dermatol*. 2006;16(5):518–522.