SHORT COMMUNICATION

A report of human papilloma virus-16 associated vaginal carcinoma after thirty-two years of successful radiation therapy for cervical cancer

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Abstract Once the recommended 5-year recurrence-free follow-up is achieved for cervical cancers regular annual pelvic examination is mandatory. The main aim of presenting this short report is to emphasize the difficulties in the collection and interpretation of cytology samples from stenosed cervix or vault after pelvic irradiation. Radiotherapy can induce changes in the cellular morphology which may persist for many years. A 64-year old post-menopausal lady who had received radiation therapy 32 years back for cervical carcinoma stage IIb presented to the Gynecology outpatient department with vaginal spotting. Even though the patient was under regular follow-up for the initial 2 years, she was lost to further follow-ups. The patient was symptom-free except for one episode of spotting in August 2016 and the histopathological examination of the vault smear had ruled out malignancy. However, 1 month later she again presented with spotting and pelvic examination revealed a warty growth at the lateral vaginal wall. The tissue excision biopsy was tested positive for HPV-16 DNA and the histopathology confirmed vaginal squamous cell carcinoma. The association of human papilloma virus (HPV) in cervical cancers was well established and these patients manifest a higher risk of

HPV-induced vaginal cancers. HPV DNA testing during follow-up may facilitate early recognition of HPV-related lower genital tract cancers.

Keywords Cervical cancer · Human papilloma virus (HPV) · Recurrence · Vaginal cancer

Human papilloma virus (HPV) infection is a well-established cause of cervical cancer. Women who have been treated for a prior anogenital cancer, particularly of the cervix demonstrates a high relative risk of being diagnosed with vaginal cancer [1]. The main high-risk HPV, associated with vaginal intraepithelial neoplasia (VAIN) and vaginal squamous cell carcinoma is HPV-16 [2]. The vulvovaginal cancers such as verrucous carcinomas, non-keratinizing squamous cell carcinomas, condylomatous carcinomas and the vaginal squamous-transitional carcinomas often demonstrate HPV-association [3–6].

We present a report of vaginal carcinoma with HPV DNA association in a 64-year old widow who had received radiation therapy, 32 years back for cervical carcinoma. A 64-year-old post-menopausal lady with Type II diabetes mellitus, Hepatitis B positive status presented to Gynecology OPD with painless vaginal spotting and intermittent blood-stained vaginal discharge. She was diagnosed with cervical squamous cell carcinoma stage IIb, 32 years back and was treated by radiation. Even though the patient was under regular follow-up for the initial 2 years, she was lost to further follow-ups. She was symptom-free except for one episode of spotting in August 2016 and the histopathological examination of the vault smear had ruled out malignancy. However, after 1 month the patient again presented with painless spotting and there were no associated bladder or bowel disturbances. On local

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examination, a warty friable growth of about 3×2 cm size, extending from 6 to 11 o'clock position which bled on touch was noted at the lateral vaginal wall (Fig. 1). The cervix was not visualised as a result of post-radiation stenosis and the vault appeared healthy. The inguinal lymph nodes were not palpable and rectal mucosa was free. An excision biopsy from the growth was sent for histopathologic examination and part of the tissue was transported in sterile normal saline at $4-8^\circ\text{C}$ to Manipal Centre for Virus Research. The viral DNA was extracted from the processed tissue sample using Qiagen viral DNA extraction kit (QIAamp[®] DNA Mini Kit, Germany) as per manufacturer's instructions. Multiplex real-time PCR was employed for the amplification of the LCR/E6/E7 regions of HPV genome [7]. The tissue excision biopsy was tested positive for HPV-16 DNA and the histopathology confirmed vaginal squamous cell carcinoma. Histopathology revealed papillary fragments lined by multiple layers of squamous epithelium showing koilocytic atypia, loss of polarity, varying degree of dysplasia ranging from low to high-grade dysplasia and focal in situ malignancy with dyskeratosis and keratin pearls (Fig. 2). The focal invasion was observed with necrosis and tumour giant cells.

MRI of abdomen and pelvis showed eccentric wall thickening (2.9×1.7 cm) of the distal vagina and right side of introitus with loss of signal intensity on the right anterior aspect due to malignant urethral infiltration. The uterus was atrophic with no obvious cervical lesions. There was no infiltration into the rectum, bladder, pelvic side-walls, inguinal nodes, iliac nodes or distant metastases. The cystoscopy showed a narrowed urethra with irregular and

Fig. 1 The figure depicts the warty growth at the lateral vaginal wall

Fig. 2 Histological section shows papillae lined with multiple layers of malignant squamous cells with few keratin pearls and focal koilocytic atypia (H&E; 200X)

pale bladder mucosa. The patient was referred for palliative chemoradiation.

In this case, even though the patient was not on regular follow up, the vault smear had ruled out malignancy 1 month back. The detection of high-risk HPV-16 might be either due to HPV reinfection or reactivation of latent HPV infection owing to impaired immunity. The cervical cancer survivors often demonstrate a higher tendency to develop HPV-related genital cancers either due to the high-risk sexual behaviour or as a result of genetic susceptibility to this oncogenic virus. The chance of reinfection was limited in this case as the patient was a widow and denied any sexual exposure since the death of her spouse 20 years back. The suppression of the adaptive immune system leads to an increase in viral DNA load at sites of prior infection resulting in reactivation of latency [8]. The impaired immunity as a result of ageing and post-menopausal status might have led to reactivation of the latent infection in this case. A study from Sweden reported higher progression-free survival rate and overall survival rate among HPV-associated cervical cancer patients. This study observed the highest survival outcome in women having HPV-16 infection in comparison with other genotypes [9].

About 30% of vaginal cancer patients give a history of cervical cancer treatment within the last 5 years [2]. By convention, any new vaginal carcinoma developing at least 5 years after the cervical cancer diagnosis is considered a *new primary lesion*. The possible mechanisms for the occurrence of vaginal cancer are either the persistence of residual disease in the vaginal epithelium following the definitive management or the growth of fresh malignant lesion as a result of raised host-specific susceptibility to HPV-induced lower genital tract carcinogenesis [10].

However, radiation therapy can induce malignant lesions which develop 10–15 years later and the risk persists for at least 40 years [11, 12]. Women receiving radiation therapy for cervical cancer, manifest a higher risk for second cancers arising from lower anogenital areas over time which persists to be elevated for more than 40 years [12]. After 5 years of recurrence-free follow-up of cervical cancer patients, annual physical and pelvic examinations are recommended [13]. The careful bimanual examination of the entire vaginal mucosa and the vulva is essential as the primary vaginal tumours tend to be multicentric.

Vaginal cancer is a rare cancer and standardised screening is often not recommended [14]. Women with vaginal squamous cell cancers tend to have five or more lifetime sexual partners, early age at sexual debut and are observed to be current smokers [1, 15]. About 82–100% of vaginal intraepithelial neoplasias and 60–90% vaginal cancers demonstrate HPV association as per epidemiological studies [1, 9]. Even after the surgical removal of the squamocolumnar junction of the cervix, the HPV-infected malignant cells may persist silently in the residual vaginal epithelium [16]. In view of the poor outcome of advanced malignancies, early identification is vital and previous studies have examined the effectiveness of the HPV DNA testing in early recognition of recurrence [17]. Radiotherapy can induce vital changes in cellular morphology which persist for many years and in such circumstances cytology has a limited role in the follow-up [18].

After completion of treatment for cervical cancer, lifetime regular annual follow up is mandatory. This short report also highlights the difficulties in interpreting cytology samples following pelvic irradiation. The incorporation of high-risk HPV DNA testing facilitates better post-treatment surveillance and early recognition of recurrence in cervical cancer survivors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Daling JR, Madeleine MM, Schwartz SM, Shera KA, Carter JJ, McKnight B, et al. A population-based study of squamous cell vaginal cancer: HPV and cofactors. *Gynecol Oncol*. 2002;84:263–70. <https://doi.org/10.1006/gyno.2001.6502>.
- Lamos C, Mihaljevic C, Aulmann S, Bruckner T, Domschke C, Wallwiener M, et al. Detection of human papillomavirus infection in patients with vaginal intraepithelial neoplasia. *PLoS ONE*. 2016;11:e0167386. <https://doi.org/10.1371/journal.pone.0167386>.
- Horn L-C, Klostermann K, Hautmann S, Höhn AK, Beckmann MW, Mehlhorn G. HPV-associated alterations of the vulva and vagina. Morphology and molecular pathology. *Pathol*. 2011;32:467–75. <https://doi.org/10.1007/s00292-011-1476-5>.
- Bogani G, Martinelli F, Ditto A, Signorelli M, Taverna F, Lombardo C, et al. The association of pre-treatment HPV subtypes with recurrence of VIN. *Eur J Obstet Gynecol Reprod Biol*. 2017;211:37–41. <https://doi.org/10.1016/j.ejogrb.2017.01.057>.
- Scott K, Trainor J, McVeigh G, Jamison J, Loughrey MB, Kelly PJ, et al. Human papillomavirus (HPV)-associated lymphoepithelioma-like carcinoma of the vagina and anal canal: a rare variant of squamous cell carcinoma. *Int J Gynecol Pathol*. 2017. <https://doi.org/10.1097/PGP.0000000000000483>.
- Boda D, Docea AO, Calina D, Ilie MA, Caruntu C, Zurac S, et al. Human papilloma virus: apprehending the link with carcinogenesis and unveiling new research avenues (Review). *Int J Oncol*. 2018;52:637–55. <https://doi.org/10.3892/ijo.2018.4256>.
- Schmitz M, Scheungraber C, Herrmann J, Teller K, Gajda M, Runnebaum IB, et al. Quantitative multiplex PCR assay for the detection of the seven clinically most relevant high-risk HPV types. *J Clin Virol*. 2009;44:302–7. <https://doi.org/10.1016/j.jcv.2009.01.006>.
- Maglennon GA, McIntosh PB, Doorbar J. Immunosuppression facilitates the reactivation of latent papillomavirus infections. *J Virol*. 2014;88:710–6. <https://doi.org/10.1128/JVI.02589-13>.
- Larsson GL, Helenius G, Andersson S, Sorbe B, Karlsson MG. Prognostic impact of human papilloma virus (HPV) genotyping and HPV-16 subtyping in vaginal carcinoma. *Gynecol Oncol*. 2013;129:406–11. <https://doi.org/10.1016/j.ygyno.2013.02.004>.
- Berek JS. Cervical and vaginal cancer. In: Berek's Novak's Gynecol. 15th edn. Lippincott Williams and Wilkins; 2015, p. 1340–4.
- Boice JD Jr. Ionizing radiation. In: Cancer Epidemiology and Prevention, 3rd edn. Oxford University Press, USA; 2006.
- Chaturvedi AK, Engels EA, Gilbert ES, Chen BE, Storm H, Lynch CF, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. *J Natl Cancer Inst*. 2007;99:1634–43. <https://doi.org/10.1093/jnci/djm201>.
- Elit L, Fyles AW, Oliver TK, Devries-Aboud MC, Fung-Kee-Fung M. Follow-up for women after treatment for cervical cancer. *Curr Oncol*. 2010;17:65–9.
- Khan MJ, Massad LS, Kinney W, Gold MA, Mayeaux EJ, Daragh TM, et al. A common clinical dilemma: management of abnormal vaginal cytology and human papillomavirus test results. *Gynecol Oncol*. 2016;141:364–70. <https://doi.org/10.1016/j.ygyno.2015.11.023>.
- Madsen BS, Jensen HL, van den Brule AJC, Wohlfahrt J, Frisch M. Risk factors for invasive squamous cell carcinoma of the vulva and vagina—population-based case-control study in Denmark. *Int J Cancer J Int Cancer*. 2008;122:2827–34. <https://doi.org/10.1002/ijc.23446>.
- Badaracco G, Savarese A, Micheli A, Rizzo C, Paolini F, Carosi M, et al. Persistence of HPV after radio-chemotherapy in locally advanced cervical cancer. *Oncol Rep*. 2010;23:1093–9.
- Song YJ, Kim J-Y, Lee S-K, Lim H-S, Lim MC, Seo S-S, et al. Persistent human papillomavirus DNA is associated with local recurrence after radiotherapy of uterine cervical cancer. *Int J Cancer*. 2011;129:896–902. <https://doi.org/10.1002/ijc.25741>.
- Stein MD, Fregnani JHTG, Scapulatempo-Neto C, Longatto-Filho A. Cervicovaginal cytology in patients undergoing pelvic radiotherapy using the Focalpoint system: results from the RODEO study. *Diagn Pathol*. 2015;10:1. <https://doi.org/10.1186/s13000-014-0231-7>.