The Role of Human Papilloma Virus in Synchronous Gynecologic Malignancies: A Report of Two Cases and Review of the Literature

Salih TAŞKIN[1], Emre Göksan PABUÇCU[2], Alper KAHRAMAN[1], İbrahim YALÇIN[1], Uğur Fırat ORTAÇ[1]

Ankara, Turkey

ABSTRACT

Aim of the paper is to investigate the suspicious role of HPV in synchronous endometrial and cervical carcinomas and to discuss the relation between HPV and endometrium epithelium. The first case is 68-year-old and the second case is 56 year-old postmenopausal woman who were diagnosed with invasive cervical carcinoma synchronously with endometrial carcinoma. Following surgical procedures, high risk HPV DNA analysis using PCR were undertaken in both cases to investigate the possible role of HPV in synchronous malignancies. All endometrial samples were considered as negative for high risk HPV types however all cervical samples were considered as positive. Unlike cervical pathologies, HPV does not seem to play active role as etiologic agent in endometrial neoplasms, even detected synchronously with invasive cervical cancers.

Keywords: Cervical carcinoma, Endometrial carcinoma, Human papilloma virus, Synchronous cancer

Gynecol Obstet Reprod Med 2015;21:46-48

Introduction

Human Papilloma Virus (HPV) has been widely associated with several pathologies in female genital tract since accurate detection techniques have been established. Cervix epithelium is well-known host for the virus; nevertheless pathologies involving ovaries and endometrium has not been clearly associated with HPV yet. Within this perspective, two cases of synchronous malignancies were reported and the role of HPV as an etiologic factor for such cases is discussed with review of the literature.

Case 1

A 68 year-old postmenopausal woman was admitted with bloody discharge ongoing for 10 days. Physical and gynecological examination was unremarkable except for an enlarged uterus. The result of recent Pap test was negative for malignancy, which was performed 6 months ago. Transvaginal sonography (TVS) revealed irregular cystic endometrium and then biopsy was performed. Atypical cells consistent with endometrial adenocarcinoma were reported. Following magnetic resonance imaging (MRI) demonstrated multifocal cystic lesion in the uterine cavity with asymmetrical thickening of the upper portion of the corpus along with normal sized pelvic and para-aortic lymph nodes. Total abdominal hysterectomy and bilateral salpingo-oophorectomy with bilateral pelvic-paraaortic lymph node dissection were performed. Microscopic examination of the endometrium revealed a well-differentiated endometrioid adenocarcinoma in the upper portion of the endometrial cavity with less than 50% myometrial invasion and without lympho-vascular space invasion (LVSI) (FIGO 2009 classification, stage IA). Excised nodes were all considered as tumor free. Well-differentiated squamous cell carcinoma of the cervix (SCCC) (FIGO stage IA1) without LVSI was reported simultaneously within operation material. Severe koilocytosis was detected in cervical epithelium but not in the endometrium. Single polymerase chain reaction (PCR) analysis was carried out to investigate the incidence of both HPV 16 and 18 sequences in the endometrium and cervix tissue samples. Both HPV type 16 and 18 were detected in cervix epithelium, whereas endometrial samples were all negative for HPV DNA. The patient is alive and disease free for 83 months.

Case 2

A 56 year-old postmenopausal woman was admitted with the Pap test result of "high-grade squamous intraepithelial lesion (HGSIL)" that was detected during routine screening. Her medical history, physical examination and TVS were unremarkable. Colposcopy with endo-cervical curettage was

[1] *Ankara University School of Medicine Department of Obstetrics and Gynecology, Ankara*

[2] *Karaman State Hospital Department of Obstetrics and Gynecology, Karaman*

Address of Correspondence: *Alper Kahraman*
Ankara University School of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey
alper.k@hotmail.com

Submitted for Publication: *20. 01. 2014*
Accepted for Publication: *11. 04. 2014*

performed and multiple biopsies were obtained from suspicious regions and aceto-white zones of the cervix. Pathologic examination revealed a well-differentiated SCCC (FIGO 2009 classification, stage IA1), while endo-cervical sampling was considered as tumor free. Following simple hysterectomy, final pathology report confirmed stage IA1 SCCC without LVSI and synchronous stage IA (FIGO 2009) endometrioid type endometrium carcinoma. Severe koilocytosis were present in cervix epithelium and both HPV types 16 and 18 were detected as well. Unlike cervical specimens, endometrium samples were negative for both types of HPV. The patient is alive and disease free for 106 months.

Discussion

It is a well-established fact that HPV triggers many oncogenic pathways resulting in either pre-invasive or invasive lesions in female genital tract.[1] Moreover, anus, penis, oral cavity, pharenx and skin are also potential targets for the virus and several malignancies of these regions have been linked with HPV.[2] Despite this close relation, HPV has not exactly been linked with endometrial pathologies so far. Several studies have been designed to rule out the role of HPV as an etiologic agent in endometrial neoplasms; nevertheless this relation still remains controversial. Giatromanolaki et al.[3] conducted a study investigating HPV in endometrial hyperplasias and adenocarcinomas. They detected HPV type 16 in 25% and HPV 18 in 20% of adenocarcinomas. Interestingly, they reported equal frequency of HPV that was detected in endometrial adenocarcinomas with squamous differentiation and those without squamous elements. They concluded that it might be due to the unsuitable nature of the endometrial columnar epithelium and lack of the characteristic cellular changes of infection; whereas HPV that is originated from the lower genital tract may not play role in the development of endometrial adenocarcinoma. Likewise, Fedrizzi et al.[4] compared the presence of HPV in endometrial cancers and in normal controls and finally reported that there was no difference in both groups. Furthermore, in their study HPV prevalence was similar in patients with and without squamous differentiation. From a different perspective, Vestergaard et al.[5] investigated HPV either in eutopic endometrium or in ectopic endometriotic lesions and finally they failed to demonstrate the HPV in both groups. Contrarily, Oppelt et al.[6] recently conducted a study consisting of 56 endometriosis cases and 13 non-endometriosis controls to asses the role of HPV in endometriotic lesions. They concluded that both high and medium-risk HPV types can be associated with endometriosis lesions and normal endometrium, especially along with higher cervical dysplasia or carcinoma via retrograde menstruation. In summary, they proposed that HPV infection may not be involved with the etiology of endometriosis but on the other hand, could promote transformation into a carcinoma.

Given the studies, which assess the relation between HPV and pathologic endometrium, it is hard to say that HPV triggers some pathologic processes definitely. In this perspective, synchronous cancers consisting of cervix and endometrium may be feasible subjects to assess this unclear relation since HPV DNA is detected in virtually all cases (99%) of cervical cancers.[1] Nevertheless, simultaneous primary malignancies of the female genital tract are rare with an incidence of 0.7% and the most frequent unity is endometrial and ovarian carcinoma.[7] Cervical and endometrial carcinoma unity is much more uncommon at a rate of 0.17%,[8] whereas the same unity was detected at a rate of 0.1% (in two of 1984 gynecological carcinoma cases) in our gynecologic oncology department between 2005 and 2010 (unpublished data). Since reports are very limited especially with cervical and endometrial cancers that investigate the existence of high risk HPV-DNA, there are no larger series available in the literature. In this report, all cervical specimens were positive for high risk HPV, nevertheless endometrial samples were all negative. It may be proposed that high risk HPV types that are detected within cervical epithelium are probably not responsible for further atypical changes in endometrial epithelium even in synchronous cancers. In light of the current literature, above mentioned hypothesis could be proposed to clarify this unclear relation between the virus and the endometrium: (i) HPV may not migrate to the endometrium through the cervix, (ii) the endometrium may not be a suitable host for HPV replication and maturation, (iii) the virus may not trigger oncogenic pathways in the endometrial tissue. Absence of HPV related epithelial changes in the endometrial tissue further supports this hypothesis.

Senkron Jinekolojik Kanserlerde İnsan Papilloma Virüsünün Rolü: İki Vaka Takdimi ve Literatür İncelemesi

ÖZET

Bu yazının amacı HPV'nin senkron endometrial ve servikal karsinomlardaki şüpheli rolünü araştırmak ve HPV ile endometriyum epiteli arasındaki ilişkiyi tartışmaktır. İlk vaka 68 yaşında ikinci vaka 56 yaşında endometriyal karsinom ile senkron invazif servikal karsinomu bulunan postmenopozal kadınlardan oluşmaktadır. Cerrahi işlemi takiben HPV'nin senkron malignensilerdeki muhtemel yerinin araştırılması amacıyla PCR ile yüksek riskli HPV DNA analizi yapılmıştır. Alınan tüm endometrial örnekler yüksek riskli HPV açısından negatif, alınan tüm servikal örnekler ise pozitif bulunmuştur. Servikal patolojileri aksine HPV servikal kanser ile senkron görüldüğünde bile endometriyal neoplazilerde etyolojik ajan olarak aktif bir rol oynamıyor gibi görünmektedir.

Anahtar Kelimeler: Servikal karsinom, Endometriyal karsinom, Human papilloma virus, Senkron kanser

References

1. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV et. al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12-9.
2. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology 2009;384(2): 260-5.
3. Giatromanolaki A, Sivridis E, Papazoglou, Koukourakis M, Maltezos E. Human papillomavirus in endometrial adenocarcinoma: infectious agent or a mere ‘‘passenger’’? Infect Dis Obstet Gynecol 2007;31(2007):60549-53.
4. Fedrizzi EN, Villa LL, de Souza IV, Sebastiao A, Urbanetz A, Carvalho N. Does human papillomavirus play a role in endometrial carcinogenesis? Int J Gynecol Pathol 2009; 28(4):322-27.
5. Vestergaard AL, Knudsen UB, Munk T, Rosbach H, Bialasiewicz S, Sloots T. Low prevalence of DNA viruses in the human endometrium and endometriosis. Arch Virol 2010;155(5):695-703.
6. Oppelt P, Renner SP, Strick R, Valetta D, Mehlhorn G, Fasching P. Correlation of high-risk human papilloma viruses but not of herpes viruses or Chlamydia trachomatis with endometriosis lesions. Fertil Steril 2010;93(6): 1778-86.
7. Eisner RF, Nieberg RK, Berek JS. Synchronous primary neoplasms of the female reproductive tract. Gynecol Oncol 1989;33(3):335-39.
8. Ayhan A, Yalcin OT, Tuncer ZS, Gurgan T, Kucukali T. Synchronous primary malignancies of the female genital tract. Eur J Obstet Gynecol Reprod Biol 1992;45(1):63-6.