Clinical Case Report

Medicine®

OPEN

Multiple preinvasive and invasive HPV-related lesions of the anogenital tract in a female patient with HIV infection

A case report

Nicolò Clemente, MD[a,*], Lara Alessandrini, MD[b], Emanuela Vaccher, MD[c], Antonino De Paoli, MD[d], Monica Buttignol, RN[a], Vincenzo Canzonieri, MD[b], Francesco Sopracordevole, MD[a]

Abstract

Rationale: Patients with human immunodeficiency virus (HIV) infection have been shown to be at increased risk for high-risk human papillomavirus (HR-HPV) infection of the anogenital tract. Furthermore, in the last decades, the introduction of highly active antiretroviral therapy (HAART) has increased the longevity of these patients who now live long enough to develop HPV-related cancers; hence, the impact of HPV infection on HIV-positive patients is of increasing concern.

Patient concerns: We reported the case of an HIV-positive female patient on HAART with a good virological and immunological response and with a long history of HPV-related intraepithelial and invasive lesions of the anogenital tract.

Diagnoses: From 1996 to 2016, this patient was diagnosed with a high grade cervical intraepithelial neoplasia; a HR-HPV positive inguinal lymph node metastasis from clinically undetectable primary squamous cell carcinoma; a HPV-related vulvar high-grade squamous intraepithelial lesion and an invasive squamous cell carcinoma of the anus.

Interventions: All the intraepithelial and invasive lesions detected were properly treated, and subsequent follow up visits with gynecologic examination, anoscopy, pap smear and anal cytology were performed.

Outcomes: After a recurrence of the anal cancer and a subsequent salvage surgery with abdominoperineal resection, at the last available follow up visit no sign of disease recurrence was found.

Lessons: This case stresses the importance of an accurate multidisciplinary follow-up in HIV-positive patients, including not only the routine medical, immunological, and virological evaluation, but also a periodical complete examination of the anogenital tract with cervicovaginal and anal cytology, colposcopy, high resolution anoscopy, and vulvar examination.

Abbreviations: AIDS = acquired immunodeficiency syndrome, AIN = anal intraepithelial neoplasia, CIN = cervical intraepithelial neoplasia, CRT = chemoradiation therapy, CT = computed tomography, CUP = cancer of unknown primary site, FDG = fluorodeoxyglucose, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, HPV = human papillomavirus, HR-HPV = high-risk human papillomavirus, H-SIL = high-grade squamous intraepithelial lesion, LEEP = loop electrosurgical excision procedure, MRI = magnetic resonance imaging, PET = positron emission tomography, TAT = transactivator protein, VIN = vulvar intraepithelial neoplasia.

Keywords: anal cancer, HIV, HPV, HPV-related cancer

1. Introduction

Human immunodeficiency virus (HIV) infection is associated with a high incidence of several cancers,[1] and thus, Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer have been classified as acquired immunodeficiency syndrome (AIDS) defining diseases since 1993.[2] Moreover, HIV-positive patients have been shown to be at increased risk for human papillomavirus (HPV) infection[3] and, in particular, these patients have been shown to have a higher prevalence of persistent HPV infection and also a higher rate of coinfection with multiple types of high-risk HPV (HR-HPV) compared to HIV-negative individuals.[4,5] Persistent HR-HPV infection is associated with essentially all squamous cell cervical cancers, 80% to 90% of anal cancers, a high proportion of vaginal, and vulvar cancers and with nonanogenital cancers such as oropharyngeal cancer.[6] For these reasons, HIV-positive female patients are at a notably increased risk of such HPV-related malignancies.

The impact of Highly Active Antiretroviral Therapy (HAART) on HPV-related disease is currently debated, and although some studies have shown an increased regression and decreased

Editor: Akhilanand Chaurasia.

Authorship—study concept and design: NC, FS; acquisition of data: NC, LA, ADP, MB; analysis and interpretation of data: NC, LA, EV, ADP, VC; drafting of the manuscript: NC; critical revision of the manuscript for important intellectual content: EV, VC, FS.

The authors have no funding and conflicts of interest to disclose.

[a] Gynecological Oncology Unit, [b] Pathology Unit, [c] Medical Oncology, [d] Radiotherapy Unit, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, Italy.

[*] Correspondence: Nicolò Clemente, Gynecological Oncology Unit, CRO Centro di Riferimento Oncologico, National Cancer Institute, Via Franco Gallini—Aviano (PN), Italy (e-mail: nicoclemente@alice.it).

Medicine (2017) 96:4(e5948)

Received: 22 April 2016 / Received in final form: 24 December 2016 / Accepted: 30 December 2016

http://dx.doi.org/10.1097/MD.0000000000005948

incidence of HPV-related lesions,[7] others have reported no significant impact on the history of HPV-related disease.[1,8,9] However, the increased longevity granted by HAART may increase the cumulative exposure to HR-HPV as well as permit longer HPV persistence. Therefore, the impact of HPV infection on HIV-positive patients is a matter of increasing concern.[6]

2. Case presentation

We reported the case of a 50-year-old HIV-positive female patient with a long history of HPV-related intraepithelial and invasive lesions of the anogenital tract. The patient was diagnosed with HIV infection and hepatitis C virus coinfection (acquired via intravenous drug use) at 20 years of age, and was receiving HAART since 1996. The patient smoked since she was 18 years old, averaging 15 cigarettes per day.

The patient was referred to the Aviano National Cancer Institute for the first time in 1996 (at 31 years of age), because of a high-grade squamous intraepithelial lesion (H-SIL) on routine pap smear. The colposcopy-guided biopsy revealed a high-grade cervical intraepithelial neoplasia (CIN3), so the patient underwent a loop electrosurgical excision procedure (LEEP). At the time of CIN3 diagnosis, the patient was on a HAART regimen including stavudine, nelfinavir, and lamivudine; the plasma viral load was undetectable (< 20 copies/mL) and the CD4 T-cell count was 350 cell/μL. The final histopathological evaluation of the specimen removed confirmed the diagnosis of CIN3, without involvement of the cone apex or margins. The subsequent gynecologic follow-up consisted of a pelvic examination, a pap-smear, a colposcopy, and a vulvar examination every 6 months for the first 2 years, and then once a year in the following years. These follow-up examinations were completely negative until 2010.

Meanwhile, in 2000 (at 35 years of age), the patient was diagnosed with Hodgkin's lymphoma localized on her lateral cervical lymph nodes, stomach, liver, and spleen (stage IIIB). She underwent the 12 weeks Stanford V protocol chemotherapy and radiotherapy on the spleen (3600 cGy/18F).[10,11] A complete remission of the disease was achieved. At the end of the therapies, the plasma viral load was undetectable (< 20 copies/mL) and the CD4 T-cell count was 121 cell/μL.

In 2010, during the routine gynecologic examination, multiple palpable lymph nodes were detected in the left inguinal region. The subsequent surgical excision of bulky groin nodes revealed a lymph node metastasis from clinically undetectable primary squamous cell carcinoma; viral genome of HR-HPV was detected through in situ hybridization technique (INFORM HPV III Family 16 probe (B)—Ventana, Tucson, AZ) (Fig. 1). Subsequently, a complete clinical evaluation, with vaginal and rectal examination, cervical and anal cytology, colposcopy, vulvoscopy and high resolution anoscopy was performed, but no clinically detectable lesion emerged. Abdominal and pelvic ultrasounds, pelvic Magnetic Resonance Imaging (MRI), a total body computed tomography scan (CT), and an 18F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) were performed, but no primary lesion was found. So the patient underwent 3 cycles of adjuvant chemotherapy according to the Al-Sarraf protocol (cisplatin/5-fluoruracil) followed by pelvic radiotherapy (total dose 46 Gy).[12] At the end of the therapies, the plasma viral load was undetectable (< 20 copies/mL) and the CD4 T-cell count was 353 cell/μL. A follow-up PET/CT was carried out at the end of therapy and showed no abnormalities.

The subsequent gynecological/oncological follow-up visits (including anal cytology and high-resolution anoscopy) were completely negative until 2013, when a 17-mm wide pigmented and hyperkeratotic lesion on the right side of the vulva was detected. The lesion was excised with a final histopathological diagnosis of usual type (HPV-related) vulvar intraepithelial neoplasia (VIN) (Fig. 2). According to the most recent International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology,[13] such a lesion should be classified as vulvar high-grade squamous intraepithelial lesion (vulvar HSIL). The margins of the surgical specimen were clear of the disease. At the time of diagnosis, the plasma viral load was undetectable (< 20 copies/mL) and the CD4 T-cell count was 600 cell/μL.

In 2014, at 49 years of age, the patient was asymptomatic, but during the routine gynecologic examination, an area of increased thickness, approximately 2 cm in size, localized at the lower third of the recto-vaginal septum was detected through combined vaginal and rectal pelvic examination. The subsequent anoscopy revealed the presence of an ulcerated lesion at the anorectal junction, and the biopsy of the lesion showed an invasive squamous cell carcinoma of the anus (Fig. 3). Even in this case, the viral genome of HR-HPV was detected through the in situ

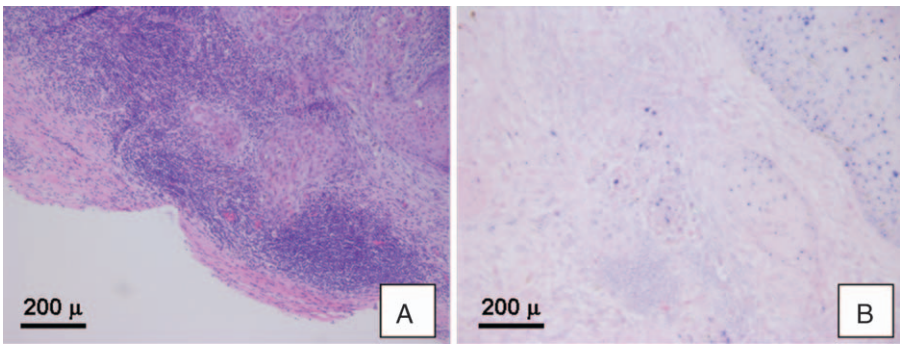

Figure 1. Metastatic islets of squamous cell carcinoma in an inguinal lymph node (A: hematoxylin and eosin; B: in situ hybridization for HR-HPV detection). The in situ hybridization technique was performed on the BenchMark Ultra automated system (Ventana, Tucson, AZ) using INFORM HPV III Family 16 probe (B) (Ventana, Tucson, AZ), which contains a cocktail of DNP-labeled HPV genomic DNA probes (high-risk oncogenic genotypes detected: 16,18,31,33,35,39,45,51,52,56,58,66). The episomal pattern appears as a large, homogeneous, globular navy-blue precipitate within the epithelial cell nucleus. The integrative pattern is a discrete, stippled navy blue nuclear pattern. Both these patterns of staining, indicating positivity for oncogenic type HPV infection, are evident in the image. DNP = dinitrophenol, HPV = human papillomavirus, HR-HPV = high-risk human papillomavirus.

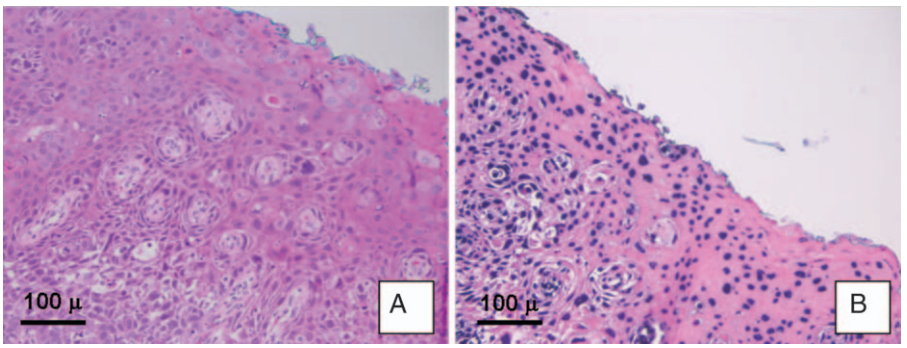

Figure 2. Vulvar high-grade squamous intraepithelial lesion (A: hematoxylin and eosin; B: in situ hybridization for HR-HPV detection). HR-HPV = high-risk human papillomavirus.

hybridization technique (INFORM HPV III Family 16 probe (B) - Ventana, Tucson, AZ). A staging PET/CT scan showed a strong FDG uptake by the distal rectum and anorectal junction as well as peri-rectal and right internal iliac lymph nodes. No other lesions were detected, and the anal carcinoma was classified as cT1 N2 M0. At the time of neoplasm diagnosis, the plasma viral load was undetectable (< 20 copies/mL) and the CD4 T-cell count was 800 cell/μL. A chemoradiation therapy (CRT) consisting of a chemotherapy regimen with Mitomycin C and capecitabine followed by pelvic radiotherapy (total dose 40 Gy) was performed as exclusive therapy, according to the most recent available guidelines.[14]

The subsequent follow-up visits, performed 6 months and 12 months after the CRT (with gynecologic examination, anoscopy, pap smear, anal cytology, and CT), were completely negative. However, 18 months after the CRT, during the routine follow-up examination, a solid mass of approximately 4 cm, with irregular margins, localized at the lower half of the recto-vaginal septum was detected. The patient was asymptomatic. The vaginal mucosa appeared undamaged, but the anoscopy revealed the presence of an ulcerated lesion at the anorectal junction and the biopsy of the lesion confirmed the recurrence of the anal invasive squamous cell carcinoma. The PET/CT scan showed a strong FDG uptake by the distal rectum and anorectal junction. No nodal involvement or other lesions were detected. A salvage surgery with abdominoperineal resection was then performed, as indicated in patients who developed recurrent anal carcinoma.[14]

At the last available follow-up visit (performed 6 months after surgery), no sign of disease recurrence was found; the plasma viral load was < 20 copies/mL and the CD4 T-cell count was 800 cell/μL.

A signed written consent was obtained from the patient for this case report.

3. Discussion

This report confirms the significant risk of developing HPV-related diseases in HIV-positive patients. In particular, in the present case, we observed the development of HPV-related preinvasive and invasive diseases in almost all the organs of the anogenital tract.

The increased incidence, prevalence, and persistence of HPV infection in HIV-positive patients is believed to be dependent on several factors. Expression of HIV proteins TAT (transactivator protein) and gp120 in the mucosal epithelium seems to be correlated with the disruption of epithelial tight junctions that could facilitate the passage of HPV 16 pseudovirions to the basal cell layer of mucosa.[15] Moreover, TAT has also been shown to upregulate E6 and E7 expression in HPV 16-positive human oral keratinocytes in vitro,[16] suggesting also a role in the development of high-grade dysplastic lesions after infection has been established. In addition, in HIV-positive patients, the depletion of CD4+ T cells inevitably determines a reduction in the cell-mediated immunity, with potential implications in the persistence of HPV infection.[17] Moreover, HIV-positive patients seem to be more susceptible to the reactivation of previously latent HPV infection, as a consequence of HIV-induced immunosuppression.[18,19]

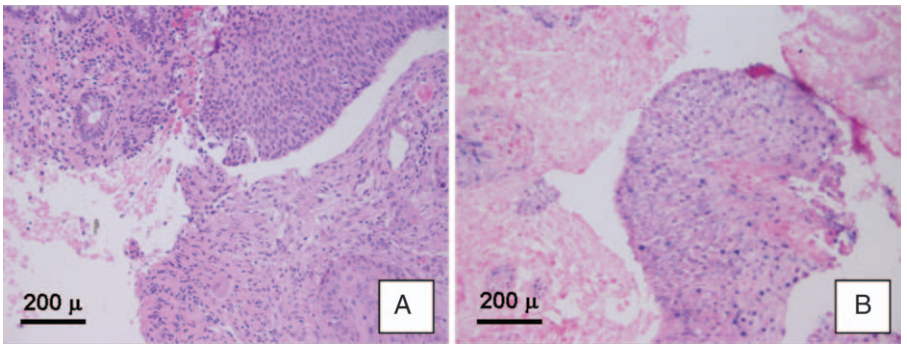

Figure 3. Squamous cell carcinoma of the anus: superficial epithelium with severe dysplasia is evident in the upper right of the image, whereas infiltrative carcinoma can be observed in the lower right. Normal intestinal glands are evident on the left (A: hematoxylin and eosin; B: in situ hybridization for HR-HPV detection). HR-HPV = high-risk human papillomavirus.

In addition to the role of persistent HR-HPV infection in the development of preinvasive and invasive diseases of the anogenital tract, other potential risk factors should be considered. Our patient, indeed, smoked since she was 18 years old. Tobacco smoke is a well-known carcinogen and is believed to influence the natural history of HPV-related cancers through several pathways in a complex manner.[20] For example, carcinogenic constituents of cigarette smoke have been shown to increase HPV viral titers and genome copies in infected cells, which potentially could enhance carcinogenesis.[21] Furthermore, tobacco smoke alters various aspects of the immune function,[22] increasing the risk of persistent HPV infection.[20]

As already underlined by Brickman and Palefsky in their recent review, the impact of HPV-related diseases in HIV-positive patients can only be expected to increase, given the magnitude of the HIV epidemic, the increased longevity of patients with HIV, and the absence of a discernible effect of HAART on the incidence of HPV-related anogenital cancers.[6] Interestingly, our patient had multiple cancers despite good virological response, confirming that the immune restoration by HAART does not seem to minimize the burden of HPV-related cancers in HIV-positive patients. [1,6,8]

In particular, the increased incidence of anal cancer in HIV-positive patients is currently a matter of concern. Squamous cell anal cancer is a rare malignancy that represents 1.5% to 2% of all the lower digestive tract cancers.[23] Unlike other common gastrointestinal malignancies, in the last decade, the incidence of anal cancer is increasing, and much of this increase is due to the rise of high-risk immunocompromised populations, including HIV-positive patients.[24] Indeed, at least a 10-fold increased incidence of anal cancer among HIV-positive patients compared to HIV-uninfected individuals is reported.[25–28] Anal cancer appears to be related to persistent HR-HPV infection in most of the cases, and the prevalence of anal HR-HPV infection is as high as 79% to 90% in HIV-positive patients.[29,30] Furthermore, given the high rate of anal HPV infection in HIV-positive patients, it is unsurprising that high-grade anal intraepithelial neoplasia (AIN), assumed as the precursor of anal invasive cancer, is also common in this group.[6] The rate of progression from high-grade AIN to invasive cancer has not been extensively evaluated;[6] moreover, this lesion is often asymptomatic, whereas the presence of anal pain, bleeding, and a palpable lesion in the anal canal are an expression of locally advanced disease. The anal intraepithelial lesions can be detected only through anal cytology and high-resolution anoscopy.[31]

Compared to other cancers, anal cancer is quite rare; thus, no support for general population screening exists,[24] but high-risk populations could benefit from appropriate screening programs, even if uncertainty on the best screening tools and algorithms remains. However, currently no national or international society formally supports routine anal cancer screening, even for high-risk populations.[24] This lack of recommendation depends on the absence of high-quality studies that demonstrate a reduced morbidity and mortality for those participating in routine screening programs.[24] Nevertheless, the New York State Department of Health AIDS Institute has begun recommending routine annual examination with anal cytology in ultra-high-risk HIV-positive patients such as those with cervical or vulvar dysplasia.[32] Notably, the European AIDS Clinical Society have recently proposed the use of anal HPV screening and cytology every 1 to 3 years in HIV-positive patients practicing anal sex, with subsequent high resolution anoscopy in the case of suspicious cytological findings.[33]

Interestingly, a lymph node metastasis from squamous cell Cancer of Unknown Primary site (CUP) was also found in our patient. CUP is an uncommon entity,[34] and cases of HIV-positive patients with CUP associated to high-grade AIN have been already reported,[35] pointing out the importance of early detection. However, in our case, all the clinical exams performed (including anal cytology and high resolution anoscopy) were negative. In such cases indeed, the identification of the primary lesion could be extremely difficult. In particular, some authors believe that anal cancer can metastasize before the primary tumor is detectable,[36] and the presence of occult microinvasive lesions of the anal canal could explain this phenomenon.

HIV-positive patients are also known to have a higher incidence of HPV-related oropharyngeal squamous cell cancers[37]; therefore, even if no formal guidelines exist, periodical examinations and health counseling (e.g., avoiding tobacco use) would be desirable in these patients.[38]

An interesting area of future research is the potential role of the HPV vaccination in HIV-positive patients. In particular, since HIV-positive patients more frequently present persistent infection with multiple HPV genotypes,[39] the introduction of the new 9-valent prophylactic vaccination could be potentially useful in these patients. Moreover, the introduction of new therapeutic vaccines could be useful as well, since they could be used in patients who have already developed HPV-related disease.[40] However, to the current knowledge, the benefits of vaccination are optimal when given before the onset of sexual activity and further studies are needed to examine the long-term efficacy of HPV vaccination in HIV-positive patients.

4. Conclusion

Our report stresses the importance of an accurate multidisciplinary follow-up in HIV-positive female patients. This follow-up should not include only the routine medical, immunological, and virological evaluations but also a complete gynecologic examination. According to the recommendations of the American college of Obstetricians and Gynecologists, HIV-positive patients should have a cervical cytology screening twice in the first year after diagnosis of HIV infection and annually thereafter.[41] However, these patients are not only at increased risk of CIN and cervical cancer, but they also have a significant risk of developing other HPV-related diseases, such as vaginal intraepithelial neoplasia (VaIN), VIN, AIN and vaginal, vulvar and anal cancers.

In our opinion, these high-risk patients should undergo not only an annual pap smear, but also a complete evaluation of the anogenital tract with pap smear, hpv test, colposcopy, vulvoscopy, anal cytology, and high resolution anoscopy soon after the initial diagnosis of HIV infection, and annually thereafter. This evaluation should be performed by gynecologists with particular expertise in the management of HIV-positive patients and in the management of preinvasive and invasive lesions of the anogenital tract. However, a multidisciplinary approach would be advisable.

Moreover, in order to reduce the burden of anal cancer in high-risk HIV patients, a widespread implementation of nation-based cancer screening programs would be desirable.

References

[1] Denny LA, Franceschi S, de Sanjosé S, et al. Human papillomavirus, human immunodeficiency virus and immunosuppression. Vaccine 2012;30(suppl 5):F168–74.

[2] Centers for Disease Control, prevention (CDC)1993 revised classification system for HIV infection and expanded surveillance case definition

for AIDS among adolescents and adults. MMWR Recomm Rep 1992; 41:1–9.
[3] De Vuyst H, Lillo F, Broutet N, et al. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prev 2008;17:545–54.
[4] Singh DK, Anastos K, Hoover DR, et al. Human papillomavirus infection and cervical cytology in HIV-infected and HIV-uninfected Rwandan women. J Infect Dis 2009;199:1851–61.
[5] Denny L, Boa R, Williamson AL, et al. Human papillomavirus infection and cervical disease in human immunodeficiency virus-1-infected women. Obstet Gynecol 2008;111:1380–7.
[6] Brickman C, Palefsky JM. Human papillomavirus in the HIV-infected host: epidemiology and pathogenesis in the antiretroviral era. Curr HIV/AIDS Rep 2015;12:6–15.
[7] Adler DH, Kakinami L, Modisenyane T, et al. Increased regression and decreased incidence of human papillomavirus-related cervical lesions among HIV-infected women on HAART. AIDS 2012;26:1645–52.
[8] Palefsky J. Human papillomavirus-related disease in people with HIV. Curr Opin HIV AIDS 2009;4:52–6.
[9] Minkoff H, Zhong Y, Burk RD, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. J Infect Dis 2010;201:681–90.
[10] Bartlett NL, Rosenberg SA, Hoppe RT, et al. Brief chemotherapy, Stanford V, and adjuvant radiotherapy for bulky or advanced-stage Hodgkin's disease: a preliminary report. J Clin Oncol 1995;13:1080–8.
[11] Spina M, Gabarre J, Fasan M, et al. Stanford V regimen and concomitant highly active antiretroviral therapy is feasible and active in patients with Hodgkin's disease and HIV infection. AIDS 2000;14:1457–8.
[12] Al Sarraf MD, El Hariry I. The role of induction chemotherapy in the treatment of patients with locally advanced head and neck cancers: a review. Gulf J Oncol 2008;4:8–18.
[13] Bornstein J, Bogliatto F, Haefner HK, et al. The 2015 International Society for the Study of Vulvovaginal Disease (ISSVD) Terminology of Vulvar Squamous Intraepithelial Lesions. J Low Genit Tract Dis 2016;20:11–4.
[14] Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol 2014;40:1165–76.
[15] Tugizov SM, Herrera R, Chin-Hong P, et al. HIV-associated disruption of mucosal epithelium facilitates paracellular penetration by human papillomavirus. Virology 2013;446:378–88.
[16] Kim RH, Yochim JM, Kang MK, et al. HIV-1 Tat enhances replicative potential of human oral keratinocytes harboring HPV-16 genome. Int J Oncol 2008;33:777–82.
[17] Van der Burg SH, Palefsky JM. Human immunodeficiency virus and human papilloma virus—why HPV-induced lesions do not spontaneously resolve and why therapeutic vaccination can be successful. J Transl Med 2009;7:108.
[18] Nowak RG, Gravitt PE, Morrison CS, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. J Infect Dis 2011;203:1182–91.
[19] Wang C, Wright TC, Denny L, et al. Rapid rise in detection of human papillomavirus (HPV) infection soon after incident HIV infection among South African women. J Infect Dis 2011;203:479–86.
[20] Jensen KE, Schmiedel S, Frederiksen K, et al. Risk for cervical intraepithelial neoplasia grade 3 or worse in relation to smoking among women with persistent human papillomavirus infection. Cancer Epidemiol Biomarkers Prev 2012;21:1949–55.
[21] Alam S, Conway MJ, Chen HS, et al. The cigarette smoke carcinogen benzo[a]pyrene enhances human papillomavirus synthesis. J Virol 2008; 82:1053–8.
[22] Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 2010;34: 258–65.
[23] Corti M, Villafañe MF, Marona E, et al. Anal squamous carcinoma: a new AIDS-defining cancer? Case report and literature review. Rev Inst Med Trop Sao Paulo 2012;54:345–8.
[24] Leeds IL, Fang SH. Anal cancer and intraepithelial neoplasia screening: a review. World J Gastrointest Surg 2016;8:41–51.
[25] Chaturvedi AK, Madeleine MM, Biggar RJ, et al. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst 2009;101:1120–230.
[26] Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010;103:416–22.
[27] Piketty C, Selinger-Leneman H, Bouvier AM, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the French hospital database on HIV. J Clin Oncol 2012;30:4360–6.
[28] Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clin Infect Dis 2012;54:1026–34.
[29] Palefsky JM, Holly EA, Ralston ML, et al. Prevalence and risk factors for anal human papillomavirus infection in human immunodeficiency virus (HIV)-positive and high-risk HIV-negative women. J Infect Dis 2001; 183:383–91.
[30] Conley L, Bush T, Darragh TM, et al. Factors associated with prevalent abnormal anal cytology in a large cohort of HIV-infected adults in the United States. J Infect Dis 2010;202:1567–76.
[31] Gimenez F, Costa-e-Silva IT, Daumas A, et al. The value of high-resolution anoscopy in the diagnosis of anal cancer precursor lesions in HIV-positive patients. Arq Gastroenterol 2011;48:136–45.
[32] New York State Department of Health, AIDS. InstituteHIV Clinical Resource: Anal Dysplasia and Cancer. New York State Department of Health, New York, NY:2007.
[33] European, AIDS, Clinical Society (EACS)European Guidelines for Treatment of HIV-positive Adults in Europe, EACS Guidelines 8.0. European AIDS Clinical Society (EACS), Copenhagen, Denmark: 2015.
[34] Joseph K, Sawyer MB, Amanie J, et al. Carcinoma of unknown primary in the inguinal lymph node region of squamous cell origin: A case series. Pract Radiat Oncol 2014;4:404–8.
[35] Gulvin J, Aboulafia DM. Squamous cell cancer of unknown primary and primary breast cancer in an HIV-infected woman: the importance of cancer screening for people living with HIV/IDS. J Int Assoc Provid AIDS Care 2016;15:194–200.
[36] Sveistrup J, Loft A, Engelholm SA. Anal cancer debuting as cancer of unknown primary. Rare Tumors 2011;3:e18.
[37] D'souza G, Carey TE, William WNJr, et al. Epidemiology of head and neck squamous cell cancer among HIV-infected patients. J Acquir Immune Defic Syndr 2014;65:603–10.
[38] Mitsuyasu RT. Non-AIDS-defining cancers. Top Antivir Med 2014; 22:660–5.
[39] Pantanowitz L, Michelow P. Review of human immunodeficiency virus (HIV) and squamous lesions of the uterine cervix. Diagn Cytopathol 2011;39:65–72.
[40] Khallouf H, Grabowska AK, Riemer AB. Therapeutic vaccine strategies against human papillomavirus. Vaccines (Basel) 2014;2: 422–62.
[41] The American college of Obstetricians, Gynecologists American college of Obstetricians, Gynecologists Committee on Practice BulletinsACOG Practice Bulletin No. 117: Gynecologic care for women with human immunodeficiency virus. Obstet Gynecol 2010;1161:1492–509.