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HIV-1 infection, but not syphilis or HBV infection, is a strong risk factor for anorectal condyloma in Asian population: A prospective colonoscopy screening study

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SUMMARY

Objective: To investigate the association between anorectal precancerous lesions, including condyloma, and sexually transmitted infections (STI) in Asian population.
Methods: This prospective study enrolled 2677 patients who underwent high-resolution colonoscopy for anorectal cancer screening. Anorectal lesions were diagnosed based on endoscopic findings and confirmed by biopsy. The association of HIV-1 infection, syphilis, and HBV infection with anorectal lesion was estimated by multivariate logistic regression. In HIV-1-infected patients (n=244), anal canal HPV-DNA was screened and genotyped.
Results: Although no malignancy was identified, anorectal condyloma was diagnosed in 32 (1.2%) male patients. 41% of anorectal condyloma cases had no specific lower GI symptoms. Multivariate analysis identified HIV-1 infection, but not syphilis or HBV infection, as an independent significant factor for condyloma (OR: 176.5, 95%CI 22.52-1383, p<0.001). In HIV-1 infected patients, positive type 16/18 HPV-DNA (OR: 4.766, 95%CI 1.838-12.36, p=0.001), lower CD4 cell count (per 100/μl decrement, OR: 1.056, 95%CI 1.056-1.587, p=0.013), and current smoking (OR: 3.828, 95%CI 1.486-9.857, p=0.005) were independently associated with anorectal condyloma.
Conclusions: HIV-1 infection, but not syphilis or HBV infection, was identified as a strong risk for anorectal condyloma. Anal HPV 16/18 was highly prevalent in patients with HIV-1 infection, especially in those with condyloma.

1. Introduction

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) worldwide.[1] HPV types are categorized into low-risk HPV types, which are associated with the development of condyloma acuminata, and high-risk HPV types, especially types 16 and 18, that can cause intraepithelial lesions and cervical, anal, and other cancers.[2] Condyloma is usually a benign disease resulting from infection with HPV type 6 or 11. However, anogenital condyloma causes psychosocial distress in affected individuals,[3] and becomes financial burden due to its refractoriness to conventional therapies.[4] More importantly, the association between genital condyloma and high-risk HPV infection has been widely described,[5,6] suggesting that condyloma

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is also a risk for anogenital cancer. Indeed, a Danish study reported that a diagnosis of anogenital condyloma correlated significantly with anal cancer.[7] It is also noteworthy that condyloma has been regarded as precancerous lesion,[8] and cases of direct malignant transformation of condyloma have been reported.[9,10] This is important considering that the incidence of anal carcinoma has increased significantly over the past 35 years in both men and women, and especially among HIV-negative men who have sex with men (MSM) and HIV-1-infected MSM, the incidence is 20 and 40 times higher than the general population, respectively.[11]

Screening strategies for anorectal HPV disease and the optimal management of abnormal test results remain topics of debate,[5] although digital rectal examination or exfoliative cytology using a swab is usually the method of choice for diagnosis. In this study we used high-resolution colonoscopy as a screening method. Although evidence for anorectal HPV disease screening with colonoscopy is scarce, colonoscopy provides the advantage of observing anorectal and anal canal area in detail, because inserted into the rectum, the colonoscope can be inverted towards the anus to ensure thorough direct observation under magnification.

HIV-1 infection is a well-established risk factor for anorectal condyloma.[12] Other known risks for condyloma are large number of sexual partners, the practice of receptive anal intercourse, history of STIs,[13,14] and immunosuppression.[15] However, the impact of syphilis and hepatitis B virus (HBV) infection, both of which are STIs prevalent especially among MSM in resource-rich setting,[16,17] on the prevalence of anorectal condyloma is largely unknown.

Based on the above background, the aim of this study was 1) to determine the prevalence of anal cancer and anorectal condyloma in Asian population by colonoscopy screening, and 2) to assess the association between anorectal HPV disease and STIs other than HIV-1 infection, such as syphilis and HBV infection. Patients with HIV-1 infection were also tested for anal canal infection with high-risk HPV to determine the relation between condyloma and high-risk HPV infection.

2. Methods

2.1. Study Design, Setting, and Participants

We conducted a prospective cross-sectional study in patients who underwent systematic screening for anal HPV disease with colonoscopy between September 2009 and June 2013 at the endoscopy unit of the National Center for Global Health and Medicine (NCGM), Tokyo, Japan. NCGM has one of the largest HIV clinics in Japan with >3,500 registered patients as of May 2013 [18]. The institutional review board approved this study. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Both HIV-1-infected and uninfected patients who underwent colonoscopy for clinical reasons were systematically screened for anorectal HPV disease during the study period, and were enrolled based on the following criteria: inclusion criteria (i) >17 years of age, exclusion criteria (i) did not complete the structured interview/questionnaire due to(i-i) refusal to provide consent to the study, (i-ii) unsure of their medications, (i-iii) impaired activities of daily living, and (i-iv) did not understand written documents (interview/questionnaire was conducted in Japanese); and (ii) patients on follow-up colonoscopy during the study period.

2.2. Measurements

Baseline characteristics, such as age, sex, ethnicity, and status of HIV-1 infection (defined by positive western blot test), syphilis infection [defined by positive *Treponema Pallidum* latex agglutination (TPHA) test and rapid plasma reagin (RPR) titer ≥8],[19] hepatitis B virus (HBV) infection (defined by positive hepatitis B surface antigen), and hepatitis C virus (HCV) infection (defined by positive HCV antibody), were extracted from the medical charts. At our hospital, routine screening for these four infections are conducted at the time of hospitalization or before colonoscopy.[20] In Japan, because universal vaccination against HBV has not been introduced and intervention of mother-to-child transmission has been very successful,[21] most adult cases with chronic HBV infection are considered to be sexually transmitted.[16] HCV can be sexually transmitted as well.[22] The structured interview/questionnaire was completed at the endoscopy unit on the day of colonoscopy. Patients were asked about their *1)* lifestyle habits (smoking history and alcohol consumption) and *2)* systemic steroid use for >2 weeks at the time of colonoscopy, in a face-to-face interview with the medical staff.[23] The questionnaire form included photographs of all oral steroid drugs approved in Japan. Furthermore, prescriptions and medical records were reviewed in addition to information provided by the patients to avoid under-reporting of steroid use. To evaluate lower gastrointestinal (GI) symptoms, the gastrointestinal symptom rating scale (GSRS) rating on a 7-graded Likert scale was included in the questionnaire.[24,25] The GSRS consists of 15 questions covering GI symptoms, and the following seven questions related to lower GI symptoms were used in this study: increased flatus, decreased passage of stool, increased passage of stool, loose stool, hard stool, urgent need for defecation, and feeling of incomplete evacuation. Asymptomatic patients were defined as those with grade ≤2 in all 7 questions.[23]

For patients with HIV-1 infection, CD4 cell count, HIV-1 viral load, either antiretroviral therapy (ART)-naïve or experienced, route of transmission, and the value of anti-*Entamoeba histolytica* (anti-Eh) antibody were obtained from the medical charts. For CD4 count and HIV load, we used data collected closest to and preceding up to three months the day of colonoscopy. In Japan, because the prescription period under the health care system is limited to three months, patients need to make visit at least every three months for prescription as well as monitoring CD4 cell count and HIV-1 load. Anti-Eh antibody was routinely measured at the time of endoscopy. Furthermore, immediately following colonoscopy, rectal swabs (DNAPAP cervical sampler, Qiagen, Gaithersburg, MD) were obtained from the anal canal area. Rectal samples were analyzed for HPV-DNA and genotyped by polymerase chain reaction (PCR)-invader assay, as described previously for 14 high-risk HPV types.[26] HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 were defined as oncogenic HPV,[27] with particular focus on infection with type 16 or 18, both of which carcinogenicity is well-confirmed.[28]

2.3. Diagnosis of anorectal HPV disease

An electronic high-resolution video endoscope (model CFH260; Olympus Optical, Tokyo) with full colonic preparation was used for diagnosis of colorectal disease. Well-trained staff performed colonoscopy while blinded to the questionnaire results. The location of all lesions was recorded in the electronic endoscopic database (Olympus Medical Systems; Solemio Endo). Anorectal cancer and other HPV diseases were screened for in all patients and biopsy or endoscopic mucosal resection were performed when necessary (Figure 2a-c). The biopsy or resected sample was histopathologically assessed by experienced pathologists (Figure 2d-f).[29]

2.4. Statistical analysis

Baseline characteristics were compared between patients with and without anorectal condyloma (only cases with condyloma were diagnosed as anorectal HPV disease in this study), using the