Association of Immune Status with Recurrent Anal Condylomata in Human Immunodeficiency Virus-Positive Patients

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Purpose: An anal condyloma is a proliferative disease of the genital epithelium caused by the human papillomavirus. This condition is most commonly seen in male homosexuals and is frequently recurrent. Some reports have suggested that immunosuppression is a risk factor for recurrence of a condyloma. Thus, we investigated the risk factors for a recurrent anal condyloma in human immunodeficiency virus (HIV)-positive patients.

Methods: We retrospectively analyzed 85 consecutive patients who were diagnosed with and underwent surgery for an anal condyloma from January 2007 to December 2011. Outcomes were analyzed based on clinical and immunologic data.

Results: Recurrent anal condylomata were found in 25 patients (29.4%). Ten cases (40.0%) were within postoperative 3 months. At postoperative 6 months, the CD4 lymphocyte count in the recurrent group was lower than it was in the non-recurrent group (P = 0.023).

Conclusion: CD4-mediated immunosuppression is a risk factor for recurrent anal condylomata in HIV-positive patients.

Keywords: Condyloma accuminata; Human papillomavirus; HIV; Recurrence; Immunosuppression
METHODS

The subjects of this study included HIV-positive patients who had been diagnosed as having an anal condyloma and who had been surgically treated at National Medical Center from January 2007 to December 2011. We analyzed age, gender, transmission routes, sexual behavior, the presence of highly active antiretroviral therapy (HAART), combined infectious diseases, the number of CD4 and CD8 lymphocytes, and HIV RNA copy numbers by performing a retrospective medical record review.

Surgery was performed in the prone position under spinal anesthesia by a single specialized colorectal surgeon. Large-sized or pedunculated masses were resected by examining the skin around the anus and intraanal canal with the naked eye. Meanwhile, small-sized and sessile masses were removed using the electrocautery method. An anal condyloma was confirmed by performing a histopathological examination for all patients. The follow-up for recurrence of the anal condyloma was conducted at the outpatient clinic in the first postoperative week and in the first, third and sixth postoperative months. The medical records included results acquired from regularly-performed examinations, including the number of CD4 and CD8 lymphocytes and the HIV RNA copy numbers, as well as other information from the Infectious Diseases Section of the Department of Internal Medicine. Serologic results obtained one month earlier and one month later were considered valid when comparing the diagnoses, the time of surgery, and dates of outpatient treatment for an anal condyloma.

Statistical analyses were performed using IBM SPSS ver. 20 (IBM Co., Armonk, NY, USA), and clinical manifestations, including transmission routes, sexual preference, and the presence of HAART and other associated infectious diseases, were analyzed using Pearson’s chi-square test. The number of CD4 and CD8 lymphocytes, and the HIV RNA copy numbers were analyzed using a Student’s t-test. P-values of less than 0.05 were considered statistically significant.

RESULTS

The 85 subjects were all male. Most subjects were HIV positive patients who had contracted HIV through sexual contact (98.8%), and about 2/3 of the subjects were homosexuals (70.6%). About 2/3 of the patients contracted cytomegalovirus infection associated with condyloma, and about 1/3 of the patients were confirmed with hepatitis A virus infection and syphilis (Table 1).

Recurrence was detected in 25 patients (29.4%), and the average time to recurrence was 5.1 months (range, 1.3 to 14.2 months). The recurrence rate was highest during the first three postoperative months, with recurrence in 10 patients (40.0%). Recurrence was confirmed in 7 patients (28.0%) between the third and the sixth postoperative months, and in 8 patients after the first six postoperative months. Although most patients (20 patients, 80.0%) had single recurrence, one patient (4.0%) experienced more than Table 1. Clinical characteristics of the patients

| Characteristic | Value |
|---------------|-------|
| Age (yr)      | 34.6 (19-68) |
| Gender        | Male 85 (100) Female 0 (0) |
| Mode of transmission (HIV) | Sexual contact 84 (98.8) Transfusion 1 (1.2) |
| Sexual behavior | Homosexual 60 (70.6) Heterosexual 5 (5.9) Bisexual 4 (4.7) No response 16 (18.8) |
| HAART         | Yes 45 (52.9) No 40 (47.1) |
| Coinfections  | None 16 (18.8) CMV 23 (27.1) Syphilis 8 (9.4) HAV 2 (2.4) CMV & HAV 22 (25.9) CMV & syphilis 8 (9.4) CMV, HAV, syphilis 5 (5.9) CMV, HAV, syphilis, & HBV 1 (1.2) |

Values are presented as mean (range) or number (%).

HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; CMV, cytomegalovirus; HAV, hepatitis A virus; HBV, hepatitis B virus.

Fig. 1. Lower CD4 lymphocyte count was shown in recurrent patients than in nonrecurrent patients at postoperative 6 months. HIV, human immunodeficiency virus; Dx, diagnosis; Postop., postoperative.
three recurrences. Although 52.9% of the patients received antiretroviral drug treatment, no significant differences were observed between the recurrent and the nonrecurrent groups. The coinfection rates of cytomegalovirus, hepatitis A and hepatitis B virus as associated with HPV infection were higher in the recurrent group compare to the nonrecurrent group. The infection rates of syphilis were higher in nonrecurrent group (P = 0.010) (Table 2). During the study period, similar CD8 lymphocyte numbers were observed between the two groups. On the other hand, CD4 lymphocyte numbers were low in the recurrent group throughout the study period. CD4 lymphocyte numbers in the sixth postoperative month, in particular, were identified to be statistically significant (P = 0.023) (Fig. 1). HIV RNA copy numbers exhibited no significant difference between the two groups.

**DISCUSSION**

Anal condyloma is a sexually-transmitted disease caused by the HPV. Even though it can be transmitted to any susceptible individual, it is more prevalent in HIV-positive patients. An anal condyloma is the most commonly reported anal disease in HIV-positive patients, and the occurrence of an anal condyloma is closely related to the HIV-positive patients’ immune deficiency, sexual intercourse patterns, and number of sexual partners. This research addressed the commonly-involved immune deficiencies in HIV-positive patients. The study population was all male patients who had mostly

**Table 2. Risk factor analysis of recurrent condylomata**

|                        | Nonrecurrent (n = 60) | Recurrent (n = 25) | P-value |
|------------------------|-----------------------|-------------------|---------|
| **Age (yr)**           |                       |                   |         |
| <30                    | 22 (36.7)             | 8 (32.0)          | 0.064   |
| 30-39                  | 18 (30.0)             | 15 (60.0)         |         |
| 40-49                  | 14 (23.3)             | 2 (8.0)           |         |
| ≥50                    | 6 (10.0)              | 0 (0)             |         |
| **HAART Therapy**      |                       |                   | 0.700   |
| Therapy                | 31 (51.7)             | 14 (56.0)         |         |
| None                   | 29 (48.3)             | 11 (44.0)         |         |
| **Coinfections, n/answers (%)** |              |                   |         |
| CMV                    | 37/57 (61.7)          | 21/25 (84.0)      | 0.082   |
| HAV                    | 15/58 (25.0)          | 12/25 (48.0)      | 0.050   |
| Syphilis               | 21/59 (35.0)          | 2/25 (8.0)        | 0.010   |
| HBV                    | 4/60 (6.7)            | 4/25 (16.0)       | 0.189   |
| **CD4 lymphocyte counts (cells/mm²)** |            |                   |         |
| At HIV diagnosis       | 350 ± 175             | 294 ± 139         | 0.386   |
| At condyloma diagnosis | 364 ± 177             | 293 ± 121         | 0.088   |
| Postoperative (3 mo)   | 426 ± 163             | 351 ± 149         | 0.058   |
| Postoperative (6 mo)   | 419 ± 176             | 329 ± 137         | 0.023   |
| **CD8 lymphocyte counts (cells/mm²)** |            |                   |         |
| At HIV diagnosis       | 823 ± 369             | 834 ± 254         | 0.877   |
| At condyloma diagnosis | 868 ± 449             | 866 ± 417         | 0.676   |
| Postoperative (3 mo)   | 1,013 ± 546           | 1,012 ± 704       | 0.486   |
| Postoperative (6 mo)   | 896 ± 387             | 838 ± 373         | 0.650   |
| **HIV RNA copies (copies/mL)** |                  |                   |         |
| At HIV diagnosis       | 51,283 ± 170,533      | 36,695 ± 114,547  | 0.287   |
| At condyloma diagnosis | 40,530 ± 152,106      | 28,497 ± 103,579  | 0.355   |
| Postoperative (3 mo)   | 7,392 ± 20,546        | 3,393 ± 13,130    | 0.513   |
| Postoperative (6 mo)   | 10,250 ± 32,062       | 3,391 ± 11,401    | 0.574   |

Values are presented as number (%) or mean ± standard deviation unless otherwise indicated. HAART, highly active antiretroviral therapy; CMV, cytomegalovirus; HAV, hepatitis A virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.
contracted HIV infection through sexual contact. Among those, 60 out of the 85 patients (70.6%) indicated that they were homosexuals, and a considerable number of nonrespondents were assumed to be homosexuals. Although a direct investigation was not conducted, HPV infection was thought to have been transmitted through anal sexual intercourse. According to Hwang et al. [11], greater numbers of male patients were prone to anal diseases in HIV-infected patients than in those without HIV infection. Moreover, homosexual intercourse was reported to be significantly higher in terms of transmission routes.

An anal condyloma reportedly has a recurrence rate of 20 to 50%, and surgical treatment is generally known to have low recurrence rates. However, depending on the particular study, the values vary [1, 2]. The postoperative recurrence rate was about 30% in this study. About 20% of the 30% with recurrence were intractable anal condyloma patients showing repeated recurrences after surgical treatment. Factors involved in the recurrence are anticipated to be reinfection from repeated sexual contact, postoperatively-remaining lesions, and reappearance of lesions caused by latent viruses in the body.

An anal condyloma is a disease spread through direct sexual contact. Hence, the incidence and recurrence rates have been reported highly in individuals with frequent sexual contacts and multiple sexual partners [4, 5, 10]. Thus, a considerable number of patients with recurrence have the possibility of reinfections. Although reinfections were thought to be included in this study, II, the possibility of reinfections was not recorded in the interviews with recurrent patients. In terms of the technical aspects of surgery, a single specialized surgeon performed all operations, and no differences were shown in the recurrence rates over time. Thus, this was considered an insignificant factor.

Cell-mediated immunity is associated with the reappearance of asymptomatic and latent infections. Previous studies have already verified the fact that cellular immunity is involved in HPV-induced lesions and have reported that anal-condyloma prevalence is more common in HIV-positive patients and transplant recipients managed with immunosuppressants [9, 12-15].

HPV generates the transformation of Langerhans cells, which play an essential role in the local cutaneous immune response, and sustains infections by consuming CD4 cells, CD16 (macrophages/natural killer cells) cells, and CD1a (Langerhans cells) cells in infected sites. These local responses are profoundly related to a weakened immune system of the whole body [9]. Le Poole et al. [6] presented evidences of immunosuppression, including decreases in transporters associated with antibody expression and dendritic cells, increases in interleukin-10 production by analyzing immunological indicators in anal condyloma lesion patients without HIV infections or other immunosuppressive treatment.

In this study, we planned the research by taking into account the possibility that different factors affecting the immunity of HIV-infected patients might influence the recurrence of an anal condyloma. However, CD8 lymphocytes, HIV RNA copies, antiretroviral treatment, and other variables were not related with recurrence; however, the number of CD4 lymphocytes was found to be lower in the recurrent group than in the non-recurrent group. Because CD4 lymphocytes are excellent indicators reflecting the immunity condition of HIV-infected patients, the condition of the immune system of a patient should be associated with the recurrence of disease. However, statistically significant differences were shown only after the sixth postoperative month and did not completely coincide with the recurrent times of the patients.

A high prevalence of syphilis was exhibited in the nonrecurrent group. This was attributable to the inclusion of positive responders in qualitative test and did not reflect current infections. Critchlow et al. [16] reported that compared to non-HIV-infected patients, HIV-infected patients rarely shifted from positive to negative responses after HPV infections. The outcome was thought to be attributable to diminished responses generated by concurrent infections with various HPV subtypes or usual treatments. Moreover, a domestic study [17] reported that high-risk and multiple HPV infections were more frequently detected in HIV-infected patients than in patients without HIV infection. Thus, further study on the relationship between HPV subtypes and recurrence is thought to be essential. In addition, Mistrangelo et al. [7] reported that recurrence rates declined in the group administered with plants known to enhance the postoperative immunity of patients who had undergone anal condyloma surgery. In this regard, further studies on the application of immune-regulating substances pre- and postoperatively are expected to produce favorable results.

In conclusion, a marked decrease in CD4 lymphocytes was observed in the recurrent group compared to the nonrecurrent group with respect to anal condyloma in HIV-positive patients. Thus, diminished immunity mediated by CD4-related cells is thought to affect the recurrence of an anal condyloma.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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