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Review Article

Complicating factors in the management of condyloma acuminata in HIV patients

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Abstract Condyloma Acuminata (CA) is an infectious disease with clinical manifestation of vegetation/ hyperkeratotic growth in the mucosal area and anogenital skin. More than 90% of CA cases are caused by infection of Human Papilloma Virus (HPV) type 6 or 11. Management of CA includes surgical and non-surgical therapy. However, the conventional therapy for CA have high recurrence rate, which ranges from 50-60%. Immunocompromised patients, including people with Human Immunodeficiency Virus (HIV) have higher recurrency rates compare to healthy people. Other matter arising in the management of CA in HIV patients is its resistance to conventional therapy. Success rate of CA therapy in HIV patients is related to the patient's immune response, low zinc levels in blood and also their CD4 levels.

Key words
Condyloma acuminata, HIV, HPV, immune response, zinc.

Introduction

Human papillomavirus (HPV) is a viral infection, mostly transmitted sexually and can cause malignant cancer or benign tumors of the skin and mucosa.[1] This virus has double-strain DNA, without a capsule and belongs to the papilloma family with more than 170 subtypes and there are new types that are constantly being discovered. The most frequent HPV type to be infected are HPV type 6, 11, 16, and 18. People infected with type 6 and 11 often experience benign lesions, while those infected with types 16 and 18 mostly had malignant lesions.[2]

Condyloma acuminata (CA) is an infectious disease in the form of vegetation on the mucosal area and anogenital skin. Nearly more than 90% of KA cases are caused by HPV type 6 or 11. Areas of predilection of CA include the vulva, perineum, perianal, vagina, cervix, penis, anus, scrotum and urethra.[2,3] Based on a systematic review of 32 epidemiological studies of CA worldwide, the reported incidence of CA ranges from 100-200 new cases per 100,000 adult population each year. The number of CA patients in Dr. Sardjito Hosipatl Yogyakarta in 2019 was 31% of the total number of patients seeking treatment at a sexually transmitted infection (STI) clinic.[1,4]

CA management can be divided into two types, namely surgical and non-surgical. Surgical interventions include excision, electrocautery, cryotherapy, and laser. Non-surgical therapies include podophyllin, podophyllotoxin, trichloroacetic acid, chemotherapy agents, or immunotherapy. The problem in CA management is the high recurrence rate, ranges from 50-60%.[5,6] The severity of dysplasia, HPV subtypes, and the pattern of sexual intercourse have been suggested as causes of CA recurrence. In many studies, it was also found that the

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prevalence and recurrence of CA was higher in immunocompromised patients including HIV patients than in healthy population.[7] HIV infection has been shown to support reactivation and expression of latent HPV infection, and correlates with the patient's degree of immune deficiency. In addition, HIV infection can cause dysplastic degeneration that is more frequent in women with cervical HPV lesions. This risk increases from 1% in healthy (HIV negative) patients to 20% in HIV-infected women. Panfilis *et al.* found the recurrence of CA after treatment in HIV patients was 66.4% compared to 26.8% in control subjects.[8]

This paper will focus on the complications of CA management in patients with HIV. Clinicians are expected to be able to understand the pathophysiology of CA in patients with HIV therefore appropriate therapy and education can be given, in regard to their disease condition.

Condyloma acuminata in HIV patients

Several studies found that the prevalence of HPV infection including CA in patients with HIV is higher than non-HIV patients.[7,8] Low *et al.*, in 2011 reported that the incidence of CA in HIV positive patients was 5.01 people per year compared with 1.31 people per year in HIV negative patients. In addition, this study also found that HIV seropositive women with $CD4^+ \leq 200/mm^3$ had a 20 times higher risk of CA than HIV seronegative women. Meanwhile, HIV seropositive women with $CD4^+ > 200/mm^3$ had a risk CA 6 times greater than HIV seronegative women.[9]

The morphology of CA lesions in HIV patients was found to be no different from the morphology of CA in non-HIV patients. Aynaud *et al.* found that the morphology of CA lesions in HIV patients was similar to non-HIV patients. CA lesions were predominantly exophytic, namely 85.1% in HIV patients and 84.2% in non-HIV patients. In addition, it was found in HIV patients that the number of CA lesions was higher, found in many locations, diffuse infection covered a total area of more than 4 cm, and often more extensive and larger than CA in non-HIV patients.[10,11] CA treatment in HIV patients was also more resistant to therapy, and had more recurrences.[10,11] Sung *et al.* found that the mean recurrence time of anal CA lesions in HIV patients was 5.1 months with a range from 1.3 months to 14.2 months.[12]

The following factors complicate the management of CA in patients with HIV.

1. Immune response to HPV

Human Papilloma Virus is an obligate intracellular, which can reproduce in the host cell. HPV DNA is a double strand virus, containing 7,900 base pairs, arranged in a circle.[13] The viral genome consists of 8 open reading frames, 6 initial genes (E1, E2, E4, E5, E6 and E7) coding for initial proteins and 2 late genes (L1 and L2) which code for late proteins. The E1 protein assists in viral replication as a host replication engine. Proteins E5, E6 and E7 are thought to be associated with avoidance of virus from the immune system. Activation of E4 protein will induce amplification of viral genome replication, increasing the number of viral copies per cell in large numbers. The E5 product can downregulate the histocompatibility leucocyte antigen (HLA) of infected cells, facilitating the avoidance of the virus from the immune system.[14,15] E6 and E7 are considered tumorigenic genes, their products can bind to the tumor suppressor protein p53 and stop the cell cycle, disrupt apoptosis of infected cells and promote transformation. The L1 and L2 proteins are responsible for forming the structural components of the viral capsid. E2 help set the transcription of E6 and E7. The integration of

the HPV genome into the host genome will disrupt the function of E2 regulation, leading to uncontrolled expression of E6 and E7, which promotes the development of normal cell cycle disorders and carcinogenesis.[16]

During the early stages of HPV infection, the innate immune response becomes the first line of defense against infection. Dendritic cells (DC), langerhans cells (LC), natural killer cells (NK), natural killer T cells (NKT) and keratinocytes are important in promoting adaptive immune responses. Most of these cell types can promote cytokine-mediated proinflammatory processes, which link the innate immune response to the adaptive immune response. Natural immune mechanisms against HPV infection with keratinocytes that are capable of producing transforming growth factor β (TGF-β), tumor necrotizing factor (TNF), interferon (IFN) α and β which can inhibit HPV replication in keratinocytes infected by HPV, including inhibiting protein E6 and E7. In addition, NK cells can immediately eliminate HPV-infected cells.[17] NK cells can recognize infected cells without expressing major histocompatibility complex (MHC)-I. Langerhans cells and dendritic cells have an important role in adaptive or specific immunity because of their ability to capture antigens and then present them to naïve T cells. T cells will then differentiate to produce a number of cytokines, chemokines, and adhesion molecules at the infected site. Persistent HPV infection indicates a reduced local and systemic cellular immune response. [17]

HIV infection attacks the $CD4^+$ T lymphocytes, damaging patient's immunity and making the patient more susceptible to various infections.[19] In people with HIV infection there is a decrease in the number of Langerhans cells, $CD4^+$ cells, macrophages, neutrophils, and NK cells, causing changes in immunity that modulate HPV infection in the tissue.[20] Chaturvedi *et al.* demonstrated that the incidence of HPV was found higher in patients with lower CD4 cell counts, and HPV virus was frequently detected among immunosuppressive conditions. Circulating memory T cells against specific HPV are also reduced in the presence of HIV infection.[21]

In general, HPV-related lesions have a higher frequency in immunocompromised persons including HIV. This is due to the direct interaction between HIV and HPV and/ or indirect immune suppression caused by HIV. Experimental evidence demonstrates the effect of the HIV-tat gene on HPV transcription. HIV-tat can also affect several other cellular functions.[22] However, the coexistence of HPV and HIV has never been found in keratinocytes, although HIV can temporarily replicate in keratinocytes, in vitro. The main targets for HIV in the skin are Langerhans cells, $CD4^+$ T cells and macrophages.[23]

Arany *et al.* compared the molecular characteristics of penile condyloma of immunocompetent individuals compared with individuals with HIV. The research was conducted using polymerase chain reaction (PCR) and reverse transcriptase (RT) techniques. The results revealed that HIV seropositive patients had multiple HPV infections and the appearance of an oncogenic HPV type that was dependent on CD4 cell count. HIV infection also changes the transcription patterns of HPV in favor of transcription of early genes such as E7.[24]

A study by Low *et al.* Found an association between decreased $CD4^+$ count and increased viral load in HIV patients.[9] The study by Wiraguna *et al.* also reported that HIV seropositive women with $CD4^+$ counts $\leq$ 200 cells/mm^3 tended to have severe CA compared to those with $CD4^+$ counts > 200 cells/mm^3.[9,33]

2. Serum Zinc Levels

Zinc is an essential element for growth, development, and maintenance of immune function. Zinc deficiency affects up to a quarter of the population in developing and developed countries as a result of lifestyle, age, and disease-mediated factors. Zinc status is an important factor that can affect antiviral immunity, particularly as zinc-deficient populations are often most at risk of contracting viral infections.[26]

Sufficient zinc status is required for maturation of T cells in the thymus and the functioning of peripheral lymphocytes. Zinc deficiency reduces the number of peripheral and thymus T cells, as well as their proliferation in response to phytohemagglutinin. In addition, there is a decrease in the function of T helper (TH) and cytotoxic T cells, and indirectly reduce the level of active serum timulyn. At the molecular level, zinc stimulates autophosphorylation of the protein tyrosine kinase Lck by non-covalent interactions with the cytoplasm of CD4 and CD8, which leads to T cell activation. Other cells are also affected, leading to reduced antibody production and cell function of the innate immune system, such as NK cell activity, cytokine production by monocytes, chemotaxis and neutrophil granulocyte oxidative explosion.[27]

In addition, zinc has unique and distinct antiviral properties against a number of human viruses. Zinc in this latest study has also been shown to contribute to innate and adaptive immune signaling pathways that have been comprehensively reviewed. Although mechanical studies are still limited, zinc appears to inhibit the enzymatic processes of proteases and polymerases, as well as physical processes such as virus assembly, infection, and uncoating.[28]

In HPV infection, therapy with exogenous zinc (CIZAR, zinc chloride and anhydrous citric acid) can effectively inhibit the production of E6 and E7 viral oncogenic proteins. The mechanism by which zinc downregulates E6 and E7 is not known yet, but may be preceded by a blockade of a component of the viral life cycle. A recent systematic review concluded that zinc supplementation was effective as a systemic treatment for skin and genital warts. Individuals with persistent warts are often zinc deficient or have lower concentrations than healthy individuals.[29,30]

Patients with HIV infection often develop zinc deficiency. Research conducted by Madueke *et al.* compared plasma zinc levels in subjects with HIV infection and without HIV infection found that the mean plasma zinc levels in subjects with HIV infection (88.35±5.49) were lower than those in subjects without HIV infection (122.62±8.57) with p value <0.001.[30] A previous study by Baum, found as many as 56% of subjects with HIV infection, had zinc deficiency (plasma zinc level <75μg/dL).[31] Another study conducted by Koch *et al*. Stated that 51% of 228 HIV-infected adults had plasma zinc deficiency (plasma zinc level ≤65μg/dL).[32]

Wiraguna *et al*. in 2018 compared plasma zinc levels among HIV positive and HIV-negative subjects infected with CA. In that study, it was found that mean plasma zinc levels were lower in CA patients with HIV infection than in CA patients without HIV infection.[33] Therefore, zinc deficiency which often occurs in HIV patients is one of many factors that causes the high recurrence of CA.

Conclusion

Condyloma acuminata is one of sexually transmitted infections caused by HPV, mostly caused by type 6 and 11. Management of CA is

divided into surgical and non-surgical methods. The prevalence of CA is higher in HIV positive populations compared to HIV negative populations. Treatment of CA in HIV patients is challenging due to resistance to therapy and high rate of recurrences. These factors complicating the management of CA in HIV patients are mainly associated with immune response and low levels of zinc.

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References

1. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. *BMC Infect Dis*. 2013;**13**:39.
2. Bzhalava D, Guan P, Franceschi S, Dillner J, Clifford G. A systematic review of the prevalence of mucosal and cutaneous human papillomavirus types. *Virology*.2013;445**(1-2)**:224-31.
3. Nishijima T, Nagata N, Watanabe K, Sekine K, Tanaka S, Kishida Y, *et al*. 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. *Int J Infect Dis*.2015;**37**:70–6.
4. Rumah Sakit Sardjito. Sistem Informasi HIV AIDS (SIHA) Yogyakarta. 2019.
5. Wifanto S., Bobby S, Aria K. Perianal Condyloma Acuminata: Factors that Contribute to the Recurrence. *New Ropanasuri Journal of Surgery*.2018; **3(2)**:31-3.
6. Kodner CM, Nasraty S. Management of genital warts. *Am Fam Physician.*2004; **70**:2335-42.
7. Sung JH, Ahn EJ, Oh HK, Park SH. Association of immune status with recurrent anal condylomata in human immunodeficiency virus-positive patients. *J Korean Soc Coloproctol*.2012;**28(6)**:294-8. doi:10.3393/jksc.2012.28.6.2948.
8. Panfilis D, Giuseppe; Melzani, Giulia, Mori, Giovanni, Ghidini, Alessandro, Graifemberghi, Severo. Relapses After Treatment of External Genital Warts Are More Frequent in HIV-Positive Patients Than in HIV-Negative Controls. *Sex Transm Dis*.2002;**29(3)**:121-5.
9. Low AJ, Clayton T, Konate I, *et al*. Genital warts and infection with human immunodeficiency virus in high risk women in Burkina Faso: A Longitudinal Study. *BMC Infect Dis*.2011;**11**:20
10. Aynaud, Piron D, Barrasso R, Poveda JD. Comparison of clinical, histological, and virological symptoms of HPV in HIV-1 infected men and immunocompetent subjects. *Sex Transm Inf*.1998;**74**:32–4.
11. Human papillomavirus (HPV) infection. Dalam: Morbidity and Mortality weekly report (Recommendations and Reports);Sexual transmitted disease treatment guidelines. Centers for Disease Control and Prevention.2010;**59(RR-12)**:69-74.
12. Association of Immune Status with Recurrent Anal Condylomata in Human Immunodeficiency Virus-Positive Patients. *J Korean Soc Coloproctol*.2012;**28(6)**:294-8.
13. Horvath CA, Boulet GA, Renoux VM, Delvenne PO and Bogers JP: Mechanisms of cell entry by human papillomaviruses: An overview. *Virol J*.2010;**7**:11.
14. Venuti A, Paolini F, Nasir L, *et al*: Papillomavirus E5: the smallest oncoprotein with many functions. *Mol Cancer*.2011; **10**:140.
15. Horvath CA, Boulet GA, Renoux VM, Delvenne PO and Bogers JP. Mechanisms of cell entry by human papillomaviruses: An overview. *Virol J*.2010;7:11.
16. Faridi R, Zahra A, Khan K and Idrees M: Oncogenic potential of human papillomavirus (HPV) and its relation with cervical cancer. *Virol J*.2011;**8**:269.
17. Renoux V.M., Bisig B., Langers I., Dortu E., Clemenceau B., Thiry M., Deroanne C., Colige A., Boniver J., Delvenne P., Jacobs N. Human papillomavirus entry into NK cells requires CD16 expression and triggers cytotoxic activity and cytokine secretion. *Eur. J. Immunol*.2011;**41**:3240–52.
18. Amador-Molina A, Hernández-Valencia JF, Lamoyi E, Contreras-Paredes A, Lizano M. Role of innate immunity against human papillomavirus (HPV) infections and effect of adjuvants in promoting specific immune response. *Viruses*.2013;**5(11)**:2624-42.
19. Murtiastutik D. AIDS. Dalam: Barakbah J, Lumintang H, Martodihardjo S, editors. Buku Ajar Infeksi Menular Seksual.

Surabaya: Airlangga University Press; 2008. h. 211-20.

20. Kobayashi A, Greenblatt RM, Anastos K, *et al.* Functional atrributes of mucosal immunity in cervical intraepithelial neoplasia and effect of HIV infection. *Cancer Res*.2008;**64**:6766-74.
21. Chaturvedi AK, Madeleine MM, Biggar RJ, *et al.* Risk of human papillomavirus–associated cancers among persons with AIDS. *J Natl Cancer Inst*.2008;**101**:1120-30.
22. Tornesello ML, Buonaguro FM, Beth-Giraldo E, *et al*. Human immunode® ciency virus type 1 tat gene enhances human papillomavirus early gene expression. *Intervirology*.1993;**36**:57-64.
23. Blauvelt A, Katz SI. The skin as target, vector, and effector organ in human immunode® ciency virus disease. *J Invest Dermatol*.1995;**105**:122S-126S.
24. I Arany PhD1 and S K Tyring MD PhD. Systemic immunosuppression by HIV infection influences HPV transcription and thus local immune responses in condyloma acuminatum. *Int J STD AIDS*.1998;**9**:268-71.
25. Maywald M, Wessels I, Rink L. Zinc signals and immunity. Int J Mol Sci 2017;18(10)
26. Ibs K. H. and Rink L. Zinc-altered immune function. *J Nutr*.2003;**133**:1452S–1456S.
27. Read, Scott & Obeid, Stephanie & Ahlenstiel, Chantelle & Ahlenstiel, Golo. The Role of Zinc in Antiviral Immunity. *Adv Nutr*.2019;**10**:696-710.
28. Lazear HM, Nice TJ, Diamond MS. Interferon-λ: immune functions at barrier surfaces and beyond. *Immunity*.2015; **43(1)**:15–28.
29. Raza N, Khan DA. Zinc deficiency in patients with persistent viral warts. *J Coll Physicians Surg Pak*.2010;**20(2)**:83–6.
30. Madueke NM, Osaronowen EM, Samuel OO, *et al*. Comparative study of plasma Zinc and Selenium levels among Human Immunodeficiency Virus (HIV) positive and negative subjects. *Afr J Food Sci Technol*. 2015;**6**:253-8.
31. Baum MK, Campa A, Lai S, *et al*. Zinc status in human immunodeficiency virus type 1 infections and illicit drug use. *Clin Infect Dis*.2003;**37**:117-23.
32. Koch J, Neal E, Schlott M, *et al.* Zinc level and infections in hospitalized patients with AIDS. *Nutrition*.1996;**12**:515-8.
33. Wiraguna AAGP, Andriani PI, Adiguna MS. Comparison of Plasma Zinc Levels Among HIV+ and HIV- Subjects Infected with Condyloma Acuminata. *Asian Pac J Cancer Prev*.2019;**20(3)**:943-9.