Case Report

Seborrheic Keratosis and Human Papillomavirus: A Co-Infection or an Etiology?

Hasti Savira Yudiana, Wisyanti Mian Uli Siahaan, Liza Handayani.

Abstract

Introduction:

Seborrheic Keratosis (SK) is a common benign epidermal skin tumor with unclear etiology. Besides sunlight exposure and genetic mutations, the involvement of human papillomavirus (HPV) remains controversial, whether HPV plays an etiological role or merely represents a co-infection. Understanding this relationship may influence the management of SK.

Case description:

A 59-year-old male presented with a brownish nodule on the right back that developed over five years and enlarged within the past year. Dermatological examination revealed a solitary, hyperpigmented, irregular nodule with a verrucous surface on the right posterior thoracic region. Histopathological examination showed epidermal papillomatosis and hyperkeratosis, with the presence of pseudohorn cysts and koilocytes.

Discussion:

Based on visual examination, the lesion was diagnosed as SK. Biopsy confirmed the diagnosis with the pathognomonic finding of pseudohorn cysts. However, the same tissue section also revealed koilocytes that indicated HPV infection. Previous studies have detected HPV DNA in SK lesions. It has been hypothesized that HPV may be involved in SK pathogenesis through mechanisms similar to those observed in squamous cell carcinoma (SCC). Nevertheless, unlike SCC, SK does not exhibit HPV-induced p53 gene inactivation. Other studies found higher HPV DNA levels in surface swabs than in biopsy specimens, suggesting that HPV detection may represent surface contamination or co-infection rather than a causal association.

Conclusion:

The presence of HPV in SK probably indicates a co-infection, therefore management of SK remains primarily for aesthetic purposes. No specific therapy was required, as HPV does not play a direct role in the pathogenesis of SK.

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Introduction

Seborrheic keratosis (SK), also referred to as seborrheic wart, senile wart, senile keratosis, or basal cell papilloma, is a benign epidermal tumor. It primarily affects older adults, with prevalence increasing progressively with age. Lesions may arise on any part of the body; however, they predominantly affect sun-exposed areas such as the head, neck, and upper extremities, although the trunk and lower extremities may also be affected. Seborrheic keratosis has significant diversity in clinical presentation. Lesions can be round, oval, or irregular in shape, and range in color from light brown to gray or black. Their size varies from a few millimetres to several centimetres. They may present as papules, plaques, or nodules with either a verrucous or smooth surface[1–4].

The exact etiology and pathogenesis of SK remain incompletely understood. Ultraviolet exposure, aging, and genetic mutations have been identified as contributory factors. In addition, viral infection—particularly human papillomavirus (HPV)—has been detected in several studies using polymerase chain reaction (PCR) analysis and histopathological examination. Beyond the characteristic findings of acanthosis, papillomatosis, hyperkeratosis, and pseudohorn cysts, some reports have described the presence of koilocytosis, a cytopathic change classically associated with HPV infection. These observations have led to ongoing debate regarding the role of HPV in the development of SK, whether it is a genuine causative agent or only a coincidental co-infection[3–6].

Clarifying the relationship between HPV and SK is important not only from a scientific standpoint but also for its potential therapeutic implications. Currently, treatment of SK is generally performed for symptomatic or cosmetic reasons. Should HPV be proven to play a pathogenic role, management strategies may need to address viral eradication and the prevention of HPV-induced cellular proliferation, similar to approaches used in other HPV-associated tumors[5,7].

Case Illustration

A 59-year-old male patient presented to the Dermatology and Venereology Outpatient Clinic of dr. Chasbullah General Hospital, Bekasi, with a complaint of a brownish nodule on his right upper back, first noticed

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approximately five years before his visit. The lesion was initially small in size and had gradually enlarged over the past year. No similar lesions were detected in other areas of the body. The patient reported no accompanying pruritus, pain, or bleeding. He reported frequent and prolonged sun exposure due to his outdoor occupation. He had not previously sought medical attention for this condition. The patient had no known comorbidities. He also denied any family history of similar lesions or malignancy.

On physical examination, the patient appeared mildly ill and was fully conscious (compos mentis). Vital signs were within normal limits. Dermatologic examination revealed a solitary, irregular, hyperpigmented nodule measuring approximately 1 cm × 1 cm × 0.5 cm, with well-defined borders, a verrucous surface, and a soft consistency, located on the right posterior thoracic region. An excisional biopsy was performed. Histopathological examination of the lesion was consistent with seborrheic keratosis, demonstrating papillomatosis and hyperkeratosis. Multiple pseudohorn cysts and koilocytes were also identified within the lesion.

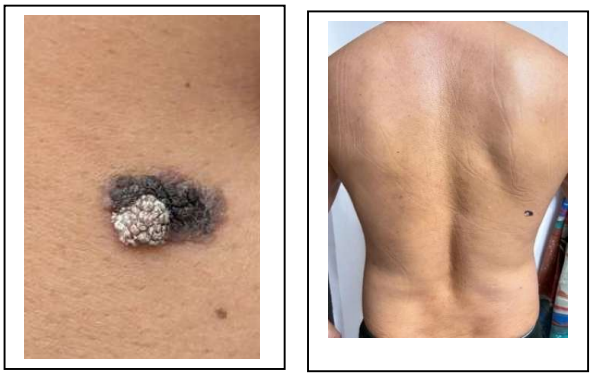

Figure 1. Brownish nodule on right posterior thoracic region

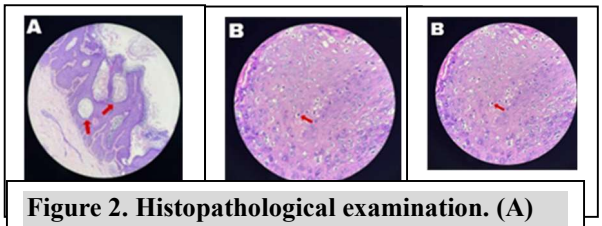

Figure 2. Histopathological examination. (A) Pseudohorn cyst (HE, 100x), (B) koilocyte (HE, 400x), (C) Papillomatosis dan hyperkeratosis (HE, 40x)

Discussion

Although the exact etiology of seborrheic keratosis (SK) is unknown, chronic sun exposure and genetic mutations are considered important risk factors. A Korean study found that sun-exposed areas, especially the face and neck, had the highest prevalence of SK, followed by the trunk. In contrast, a study from the United Kingdom found that the back was the most common site of SK across all Fitzpatrick skin types.8,9 This distribution correlates with increased expression of guanine deaminase (GDA) and amyloid precursor protein (APP), which are upregulated in aging and UV-damaged skin and have also been detected in SK lesions[5,10]. In this case, the patient was a 59-year-old outdoor worker with a lesion located on the trunk, specifically the right posterior thoracic region, consistent with commonly sun-exposed areas. The most frequently reported genetic mutation in SK is a mutation in the fibroblast growth factor receptor 3 (FGFR3) gene, found in approximately 48% of cases. Mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) follow at 32%. Both mutations promote keratinocyte proliferation, reduce apoptosis, and inhibit adhesion to the extracellular matrix. Increased activity of protein kinase B (Akt), which regulates apoptosis and the cell cycle, is also linked to SK pathophysiology[3,5,11]

In addition to ultraviolet exposure and genetic alterations, human papillomavirus (HPV) infection has frequently been suspected to be associated with SK. HPV is a double-stranded DNA virus comprising more than 200 genotypes. It is classified into mucosal and cutaneous types. Cutaneous HPV includes benign types associated with verruca vulgaris and oncogenic types linked to epidermodysplasia verruciformis (EV). Mucosal HPV is classified into high-risk types associated with cervical and other anogenital cancers and low-risk types that typically cause benign lesions[4,12].

Several previous studies have detected HPV DNA in both genital and non-genital SK lesions. A study from Japan detected HPV DNA in 30 of 104 (28.8%) non-genital SK samples using in situ hybridization (ISH). When using polymerase chain reaction (PCR) and Southern blot hybridization, HPV DNA was detected in 95 of 104 cases, with HPV 18 (83.7%) and HPV 6 (77.9%) being the most frequently identified types.4 In genital SK, Tardío et al. identified HPV DNA in 70% of cases, with 96% of them is HPV 6. Based on these findings, they presume that HPV detection in SK may not merely indicate contamination but could instead play a direct role in its pathogenesis. The role of HPV in the pathogenesis of SK is thought to be the same as the role of HPV in the pathogenesis of SCC, where the viral oncoproteins E6 and E7 inactivate the tumor suppressor protein p53, leading to dysregulated cell cycle progression and uncontrolled proliferation[12,13]. However, unlike SCC, p53 mutations have not been identified in SK.3,5 A study conducted in Padang demonstrated no significant increase in p53 expression in SK patients with positive HPV DNA[14]. These findings suggest that the role of HPV in SK may differ from its well-established oncogenic mechanisms, like SCC, and that HPV may not be directly involved in SK pathogenesis.

A study from Germany found HPV DNA in only 2 of 51 (3.9%) non-genital SK cases, leading the authors to conclude that HPV is unlikely to be a primary etiologic factor in non-genital SK[15]. A Swedish study compared HPV DNA prevalence obtained from surface swabs of SK lesions, biopsies with the stratum corneum removed, and swabs of healthy skin. HPV DNA detection was significantly higher in surface swabs (79%) compared to biopsy specimens (19%), and the prevalence on healthy skin was similar to that found on the tumor surface. These results strengthen the hypothesis that HPV detection in SK most likely represents surface contamination or coincidental co-infection rather than playing a direct pathogenetic role[16]

Based on clinical findings, this patient was diagnosed with seborrheic keratosis. Histopathological examination revealed papillomatosis and epidermal hyperkeratosis, along with pseudohorn cysts, a characteristic feature of SK. However, koilocytes—classically associated with HPV infection—were also observed within the same tissue section.4,6 Based on the existing studies, we hypothesize that the presence of HPV in the SK lesion in this case is not an etiology but only a co-infection.

Conclusion

The presence of HPV in seborrheic keratosis is most likely indicative of a surface co-infection rather than a direct involvement in tumor pathogenesis. The management of SK with HPV co-infection is generally limited to cosmetic considerations and symptomatic relief. Unlike the other tumors caused by HPV, treatment is not aimed at suppressing virus-induced cellular proliferation or eliminating infected cells.

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