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Penile squamous cell carcinoma related to high risk HPV infection

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ABSTRACT

Penile cancer is an uncommon form of malignancy, with squamous cell carcinoma (SCC) being the most common subtype. Human papillomavirus (HPV) infection is strongly associated with the development of penile SCC, particularly strains 16 and 18. This report presents two cases of penile SCC related to HPV type 18 infection and discusses the diagnosis and role of HPV in penile cancer. It aims to illustrate the clinical presentation and diagnostic challenges of penile SCC, with emphasis on the role of HPV infection. Case 1 involves a 41 yo man with a verrucous mass on the glans penis, diagnosed as well-differentiated SCC, with HPV type 18 detected. Case 2 is a 54 yo man presenting with multiple ulcerative plaques on the distal glans, also diagnosed as SCC with HPV type 18. Penile SCC can be classified into HPV-associated and non-HPV-associated subtypes. The HPV-associated SCC, more commonly seen in younger patients, is driven by viral oncogenes E6 and E7, which disrupt tumor suppressor proteins. The pathogenesis is similar to that seen in cervical cancer. Diagnosis is confirmed through histopathology and genotyping, while treatment involves surgical excision, with possible radiotherapy and chemotherapy depending on lymph node involvement. Early detection and diagnosis of penile SCC are critical for effective treatment. The HPV infection plays a significant role in the pathogenesis of penile SCC, highlighting the importance of HPV vaccination in prevention. Multidisciplinary management is essential for improving patient outcomes.

Keywords:
squamous cell carcinoma;
penile neoplasm;
HPV infection;
diagnosis;
clinical presentation

ABSTRACT

Kanker penis adalah keganasan yang jarang terjadi, dengan karsinoma sel skuamosa (SCC) sebagai subtipe yang paling umum. Infeksi human papillomavirus (HPV) sangat terkait dengan perkembangan SCC penis, terutama pada strain 16 dan 18. Penelitian ini menyajikan dua kasus SCC penis yang berhubungan dengan infeksi HPV tipe 18 dan membahas diagnosis serta peran HPV dalam kanker penis. Tujuan tulisan ini adalah untuk menggambarkan presentasi klinis dan tantangan diagnosis SCC penis, dengan penekanan pada peran infeksi HPV. Kasus 1 melibatkan pria berusia 41 tahun dengan massa verrukosa pada glans penis, didiagnosis sebagai SCC berdiferensiasi baik, dengan deteksi HPV tipe 18. Kasus 2 adalah pria berusia 54 tahun yang menunjukkan plak ulseratif multipel pada distal glans, juga didiagnosis sebagai SCC dengan HPV tipe 18. SCC penis dapat diklasifikasikan menjadi subtipe yang terkait dengan HPV dan yang tidak terkait dengan HPV. Karsinoma sel skuamosa terkait HPV, sering terjadi pada pasien yang lebih muda, dipicu oleh onkogen virus E6 dan E7 yang mengganggu protein penekan tumor. Patogenesisnya mirip dengan yang terjadi pada kanker serviks. Diagnosis dikonfirmasi melalui histopatologi dan genotipisasi, sementara pengobatan melibatkan eksisi bedah, dengan kemungkinan terapi radiasi dan kemoterapi tergantung pada keterlibatan kelenjar getah bening. Deteksi dini dan diagnosis SCC penis sangat penting untuk pengobatan yang efektif. Infeksi HPV memainkan peran penting dalam patogenesis SCC penis, yang menyoroti pentingnya vaksinasi HPV dalam pencegahan. Penanganan multidisiplin sangat penting untuk meningkatkan hasil perawatan pasien.

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INTRODUCTION

Penile cancer is an uncommon form of malignancy, with an incidence rate ranging form 0.1 to 1 per 100,000 men in high-income regions.[1] The predominant type of penile cancer is squamous cell carcinoma (SCC), though other forms of malignant penile neoplasms exist, such as basal cell carcinoma, melanoma, sarcomas, and adenosquamous carcinoma.[2] The SCC of the penis typically originates from the non-keratinized epithelium found on the glans or the inner surface of the prepuce.[3] Data collected from Dr. Sardjito General Hospital, Yogyakarta from 2019 to 2023 reported a total of 35 cases.

The main risk factors for the development of penile SCC include poor hygiene, smoking, chronic inflammation, lack of circumcision and human papilloma virus (HPV) infection.[4] A direct relationship has been demonstrated between HPV infection and penile SCC. Both conditions are directly linked to the number of sexual partners and early sexual debut. Patients with human immunodeficiency virus (HIV) have an eightfold increased risk of penile cancer development. Between 45 and 80% of penile cancer cases are associated with HPV infection, with types 6, 16, and 18 being most strongly linked.[2,4] The development of penile cancer due to HPV infection is thought to occur via the viral oncogenes E6 and E7, which are expressed in infected cells. The E6 protein interferes with the tumor suppressor gene p53, while E7 disrupts the function of RB1, another key tumor suppressor. These genes normally act to control cell growth, and their disruption can result in uncontrolled cell division and the eventual emergence of malignancy.[5]

Penile SCC is classified into various subtypes, with the most common including usual SCC (48-65%), basaloid carcinoma (4-10%), warty carcinoma (7-10%), verrucous carcinoma (3-8%), papillary carcinoma (5-15%), and mixed carcinomas (9-10%).[5] This paper reports two cases of penile squamous cell carcinoma (SCC) with positive HPV 18. The purpose of this case report is to explain the establishment of diagnosis and the role of HPV infection in penile cancer.

CASE

Case 1

A 41 yo man presented with complaints of a wound on the genital area. Since one year before the examination, the patient complained of a wound on the tip of the penis accompanied by pain. The patient consulted a general practitioner and was given antibiotics and pain relievers, but the complaint persisted. Five months before the examination, the patient complained of a spreading wound on the tip of the penis and pain. Five days before the examination, the complaint persisted and the patient consulted a dermatologist at the District General Hospital and was given clindamycin 300mg twice a day, cetirizine 10mg/d, NaCl 0.9% compress twice a day and the patient was referred to Dr. Sardjito General Hospital, Yogyakarta.

In past medical history, there were no complaints of genital wounds, the patient denied previous complaints of painful urination and discharge. In the family medical history, there were no similar complaints. In sexual history, the patient was circumcised at the age of 9 yr. First sexual intercourse occurred at the age of 17 yr with a girlfriend without using a condom. The number of sexual partners was 2, a girlfriend and a wife. Sexual orientation is heterosexual. The patient is an alcohol drinker and smoker, the patient denies ever using injected drugs, blood transfusions, or tattoos. The patient's occupation is a construction worker.

Physical examination revealed good general condition, conscious state, weight 81 kg, height 164 cm, blood pressure 127/75 mmHg, pulse 82 beats/min, respiration 18 x/per min, temperature 36.6°C. Dermatovenereological status examination found a tumor mass with multiple verrucous plaques, some with erosion on the glans penis distal third (FIGURE 1). Acetowhite examination was negative. Blood test results were within normal limits, non-reactive HbsAg, non-reactive HIV, and negative TPHA. The patient was diagnosed with a differential diagnosis of squamous cell carcinoma of the penis dd Bowen's Disease dd Giant condyloma acuminata given therapy of sodium diclofenac 2x50mg, ikagen 2 d due on erosion and planned for biopsy.

Histopathological examination results showed solid epithelial cells tumor appearance, infiltrating into the surrounding stroma. Tumor cells were of medium to large size, with abundant eosinophilic cytoplasm. Nuclei were round, oval, with coarse chromatin, and some prominent nucleoli. Keratinization in clusters (pearl horn) was observed. The stroma was infiltrated with inflammatory cells, predominantly lymphocytes. Tumor infiltrating lymphocytes 30%. Conclusion: well-differentiated squamous cell carcinoma (FIGURE 2). Genotyping also revealed HPV type 18 virus. Based on this finding, the patient was diagnosed as squamous cell carcinoma of the penis. The patient was referred to the urology department for further management. The patient is planned for partial to total penectomy by an urologist.

FIGURE 1. A tumor mass with multiple verrucous plaques, some with erosion

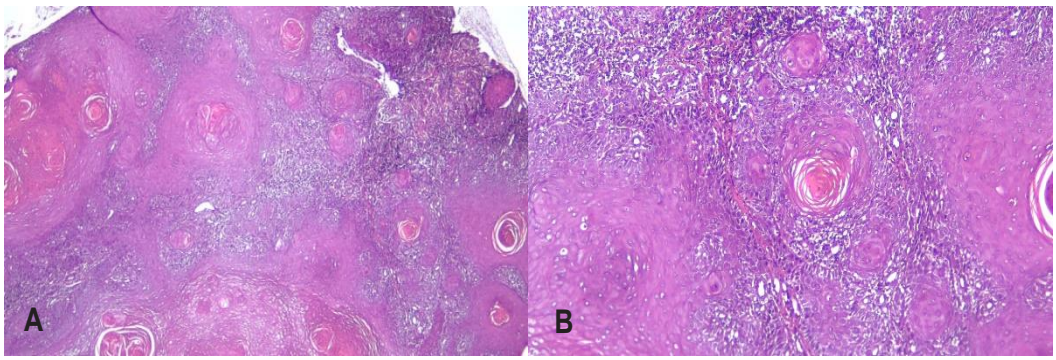

FIGURE 2. Solid epithelial cells tumor infiltrating into the surrounding stroma (A). The tumor cells were medium to large in size, with abundant eosinophilic cytoplasm (B)

Case 2

A 54 yo man presented with complaints of a wound on the genital area. Since one month before the examination, the patient complained of the appearance of pimples on the tip of the penis which then burst and became wounds accompanied by pain. The patient consulted a general practitioner and was given antibiotics ointment and oral medication. The complaint improved, and the wound dried up. Two weeks before the examination, the patient complained of the appearance of pimples that burst into wounds on the tip of the penis and spread accompanied by pain. The wound easily bled and suppurated. The patient consulted a doctor and was referred to Dr. Sardjito General Hospital, Yogyakarta.

In past medical history, there were no complaints of genital wounds, the patient denied having previous complaints of painful urination and discharge. Patient had a routine medication for hypertension with amlodipine. In the family medical history, there were no similar complaints. In sexual history, the patient was circumcised at the age of 10 yr. First sexual intercourse occurred at the age of 19 yr with his wife without using a condom. The number of sexual partners was 1, namely his wife. Sexual orientation is genital.

Physical examination revealed good general condition, conscious state, weight 81 kg, height 164 cm, blood pressure 127/75 mmHg, pulse 82 beats/min, respiration 18 x/min, temperature 36.6°C. Dermatovenereological status examination found a tumor mass with multiple verrucous plaques, some with irregular edge ulcers on the glans penis distal third (FIGURE 3). Acetowhite examination was negative. Blood examination found Hb 11.6 g/dL, leukocytes 14.2x 10^3/uL, non-reactive HIV, negative TPHA, and non-reactive HbsAg. Physical examination found the patient diagnosed with differential diagnosis of squamous cell carcinoma of the penis dd Penile Bowen's Disease dd Giant condyloma acuminata given therapy of sodium diclofenac 50mg twice/d, gentamycin ointment twice/d on erosion and planned for biopsy.

Histopathological examination results of skin tissue showed solid tumor cells with keratinization, composed of keratinocyte proliferation, infiltrating the basal membrane. Atypical tumor cells, polymorphic, generally polygonal in shape, large in size, with eosinophilic cytoplasm and increased N/C ratio. Round and oval nuclei, with irregular nuclear membranes, coarse chromatin, and prominent nucleoli. Intercellular bridges are clearly visible. Dermis is edematous, with erythrocyte extravasation, and infiltration of inflammatory cells arranged in patchy density, consisting of lymphocytes, histiocytes, and neutrophils, especially in the perivascular area. Melanin droplets were also found. Tumor infiltrating lymphocytes: +/- 60%. Conclusion: well-differentiated squamous cell carcinoma (FIGURE 4). Genotyping results showed HPV type 18 infection. Based on this, the patient was diagnosed with squamous cell carcinoma of the penis. The patient was referred to the urology department for further management. The patient is planned for partial to total penectomy by an urologist.

FIGURE 3. A tumor mass with irregular edge ulcers on the distal third of glans penis

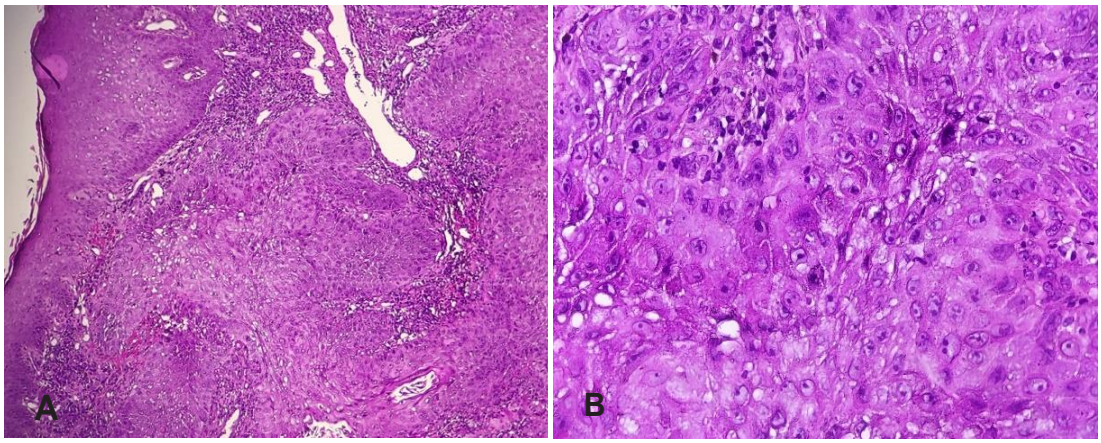

FIGURE 4. Solid tumor cells with keratinization, infiltrating the basal membrane (A). Atypical tumor cells, polymorphic, large in size, with eosinophilic cytoplasm (B)

DISCUSSION

The majority of penile cancer is SCC. It is arises from the skin of the glans or of the inner layer of the prepuce, characterized by invasive growth and early metastatic spread to lymph nodes.[5,6] There are two different etiopathogenic in penile SCC; one associated with HPV and the other one independent of HPV infection.[7] There are several recognized subtypes of penile SCC; SCC associated with HPV such as basaloid squamous carcinoma, warty carcinoma, warty-basaloid carcinoma, clear cell carcinoma, and lymphoepithelioma-like carcinoma. Some subtypes of penile squamous cell carcinoma not associated with HPV include the most common type, pseudohyperplastic, pseudoglandular, verrucous, papillary, adenosquamous, sarcomatoid, and mixed subtypes.[8]

Several risk factors contribute to the development of penile SCC, including poor hygiene, lack of circumcision, chronic inflammatory conditions, and HPV infection.[4] Additional risk factors associated with the development of penile SCC include smoking, HIV infection, poor genital hygiene, previous injury to the penis, chronic balanitis, lichen sclerosis et atrophicus, and psoralen plus ultraviolet A (PUVA) treatment to the area.[5] HPV-associated

penile SCC is more prevalent in relatively young males, who commonly refer to a high number of sexual partners and smoking history. HPV-independent penile SCC is predominant in high-income countries and affects mainly older men. The etiopathogenesis of HPV-independent penile SCC is less well understood; however, phimosis, chronic inflammation, poor personal hygiene and trauma seem to be associated factors.[7]

About one-third of penile SCC cases are associated with high-risk HPV infection, most commonly involving HPV types 16 and 18.[5,6] The second pathogenic pathway is chronic inflammation, associated with, for example, lichen sclerosus or chronic inflammation of the foreskin related to phimosis. Most penile SCCs occur in uncircumcised men. Proposed etiological factors associated with an intact foreskin are smegma and phimosis. Smegma is a product of desquamating epithelial cells and bacterial by products found between the glans penis and foreskin. Smegma-induced chronic inflammation may predispose to the development of phimosis as well as SCC.[4,6]

The pathogenesis of HPV infection in penile cancer is similar to the oncogenesis process in cervical cancer.[4] The virus initiates oncogenesis by infecting the basal layer of the penile epithelium, often entering through microtraumas or small abrasions. The HPV's capsid binds to laminin-5, allowing the virus to enter host cells. The HPV proteins E6 and E7 play a crucial role in this oncogenic process. The E6 protein causes apoptosis inactivation through intrinsic and extrinsic pathways. In the intrinsic pathway, the E6 protein will inactivate proapoptotic proteins such as p53, Bax, and Bak through the ubiquitin-proteasome pathway. In the extrinsic pathway, the E6 protein will bind to apoptosis receptors such as tumor necrosis factor receptor-1 (TNFR-1), fas-associated protein with death domain (FADD), and caspase 8. The E7 protein binds to pRb, which inhibits pRb binding to the transcription factor E2F. Activation of the E2F transcription factor will result in host cells passing through the cell cycle without stopping at the G1 phase. The E7 protein inhibits the activity of cyclin-dependent kinase inhibitors (CKIs) p21 and p27, resulting in continuous cell cycle progression. This process leads to an increase in the proliferation rate of host cells.[8]

Penile SCC typically manifests in men aged between 50 and 70 yr, with clinical symptoms ranging from small areas of erythema and induration to large ulcerative or infiltrative lesions. As the disease progresses, there may be associated itching, bleeding, discharge, foul odor, and pain. Palpation of inguinal lymph nodes is an essential part of the initial physical examination to assess potential lymphatic spread.[5] A tissue biopsy is required for pathologic diagnosis and necessary before initiation of any therapy. A biopsy can be performed by using a punch, incisional or excisional technique.[9] The diagnostic evaluation could be completed with higher local tumor definition by ultrasound or magnetic resonance imaging (MRI). The diagnostic evaluation of distant metastases could be carried out with abdominal and chest CT-scan, MRI or positron emission tomography (PET).[10]

Penile intraepithelial neoplasia (PIN) encompasses precancerous lesions of the male genital tract, including two variants: Bowen's disease (BD) and erythroplasia of Queyrat (EQ).[11] The term EQ is used for lesions over mucosal surfaces such as inner prepuce, glans, and urethra. The term BD is used when the skin of shaft of penis is affected. The BD of penis presents as well-defined, single, dull-red scaly plaques often with crusting and pigmentary changes. The BD has also been reported to arise from inguinal and suprapubic area. The

EQ is painless, very well-demarcated, bright-red, velvety, shiny, plaque-like appearance.[12] The clinical appearance of invasive penile SCC is highly variable, with manifestations ranging from an erythematous plaque or ulcer to an exophytic or verruciform tumor. The lesions, which can measure up to several centimeters in diameter, can have a stony hard or friable consistency and may bleed. They tend to be solitary lesions and can be located on any part of the penis, although they are more common on the anterior third (glans, balanopreputial sulcus, and/or prepuce).[4] In both cases, a tumor mass with multiple verrucous plaques, some with irregular edge ulcers, was found on the distal third of the glans penis, indicating a more invasive penile squamous cell carcinoma.

Another possible differential diagnosis is giant condyloma acuminata (GCA). Giant condyloma acuminata is is a rare, slow-growing verrucous tumor of the penis and anogenital region which can grow up to twenty centimeters in size and can locally destroy contiguous structures. Most studies link GCA to the low-risk HPV types 6 and 11.[13] It presents as a slow-growing cauliflower-like mass in the genital or anorectal area, with relatively slow infiltration into deeper tissues. The disease starts from a long-standing condyloma acuminatum, which can grow to sizes of more than 10 cm in diameter. Progression from the first symptoms of condyloma to GCA development may take 2.8–9.6 yr, or longer. Histologically, the tumor is characterized by papillomatosis, hyperkeratosis, parakeratosis, acanthosis, and koilocytosis.[14] In both cases, a tumor mass with multiple verrucous plaques, some with irregular edge ulcers, was found on the distal third of the glans penis, acetowhite examination are negative and the histopathologic showed a solid tumor with keratinization, composed of keratinocyte proliferation, infiltrating the basal membrane and the genotyping results showed HPV type 18 infection; indicating a more invasive penile squamous cell carcinoma.

Treatment for premalignant disease is topical agents such as 5-fluorouracil, immunotherapy with imiquimod and laser ablation therapy. Whereas localized invasive penile SCC is treated with surgical excision; alternatively radiotherapy, possibly in combination with systemic chemotherapy.[1] Lymph node involvement is the most crucial prognostic factor. Survival rates vary dramatically based on the extent of nodal involvement; 80% survival when limited to superficial, unilateral lymph nodes (N1), 10%–20% survival when nodes are bilaterally or pelvic-involved (N2/3) and <10% survival with extranodal involvement. Histologic indicators such as perineural invasion, lymphovascular permeation, and tumor differentiation also correlate with metastasis risk and mortality. Other factors that appear to influence prognosis are tumor depth, growth pattern, histologic subtype, and urethral invasion.[4] Penile SCC is a preventable disease. Patients with phimosis can undergo circumcision for cleanliness of the glans penis to prevent chronic inflammation. One of the etiologies of penile SCC is high-risk HPV infection; therefore, HPV vaccination can be administered to prepubescent boys before sexual activity.[4] Vaccination shows high efficacy in preventing HPV-related lesions in men. Vaccination containing HPV types 6, 11, 16, and 18 had an efficacy rate of 90.4% in preventing related external genital lesions. The vaccine also induces high antibody levels, much more than natural infection.[15]

CONCLUSION

We report two cases of penile SCC that tested positive for HPV 18 infection on genotyping examination.

Multidisciplinary collaboration involving urologists, dermatologists, and pathologists is necessary for early diagnosis, which enables the administration of adequate therapy that can reduce morbidity. Understanding the related risk factors for penile SCC and the role of HPV infection in penile cancer are crucial to ensure prompt and accurate management of such conditions.

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