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Multifocal HPV-Associated Anogenital Lesion: Histopathology in the Diagnosis of Penile Intraepithelial Neoplasia

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Introduction. Human papillomavirus (HPV) is a common sexually transmitted infection that can manifest as lesions ranging from benign conditions to premalignant disease.
Case. We report the case of a 37-year-old widowed man who presented with multiple nodular lesions on the penis for one year and on the anus for seven months prior to seeking medical care. The patient had a history of Hodgkin lymphoma and had previously undergone chemotherapy. Physical examination of the penile shaft and pubic region revealed multiple erythematous papules with well-defined margins, irregular borders, and variable shapes and sizes. Examination of the anal and perianal regions revealed with similar characteristics. The diagnosis was established based on histopathological evaluation, which demonstrated distinct features at the two lesion sites. Biopsy of the genital lesions revealed findings consistent with Penile Intraepithelial Neoplasia (PeIN), supported by positive p16 immunohistochemical staining and HPV genotyping positive for HPV types 18 and 45, confirming HPV-associated Penile Intraepithelial Neoplasia. In contrast, biopsy of the anal lesions showed histopathological features consistent with condyloma acuminata.
Conclusion. This report highlights the importance of clinical vigilance and the crucial role of histopathological examination in establishing an accurate diagnosis and guiding appropriate management, particularly in patients with risk factors for malignancy and a history of immunocompromised status.

Keywords: biopsy, human papillomavirus, neoplasia

Introduction

Penile intraepithelial neoplasia (PeIN) is a premalignant lesion of squamous cell carcinoma characterized by dysplastic changes in the squamous epithelium with an intact basement membrane, which distinguishes it from invasive squamous cell carcinoma. According to the World Health Organization (WHO) classification in 2022, PeIN is categorized based on its association with human papillomavirus (HPV) infection into HPV-related penile intraepithelial neoplasia and non-HPV-related penile intraepithelial neoplasia [1]. HPV-associated PeIN is reported to account for more than three-quarters of all PeIN cases [2]. The average incidence of PeIN in the Netherlands is 0.47 per 100,000 population per year. This low incidence is likely attributable to the fact that premalignant lesions are frequently unrecognized by both patients and clinicians [3].

Condyloma acuminata (CA) is a benign proliferative lesion caused by HPV, predominantly types 6 and 11; however, it may also result from mixed HPV genotypes. This condition commonly occurs on mucocutaneous surfaces or moist skin adjacent to squamous epithelium in the anogenital region, such as the cervix and anus. The clinical variants of condyloma acuminata include acuminate, keratotic, papular, and flat forms. Dermoscopic examination typically reveals characteristic features, one of which is a finger-like appearance in papillomatous lesions. Immunocompromised states have also been associated with infection by multiple HPV genotypes [4-5].

This case report aims to describe the clinical findings in a patient with Hodgkin lymphoma who presented with anogenital lesions that were clinically suggestive of condyloma acuminata; however, histopathological examination demonstrated the presence of both a premalignant

penile lesion (PeIN) and a benign anal lesion consistent with condyloma acuminata. This case underscores the importance of clinical vigilance, particularly in immunocompromised patients, and emphasizes the crucial role of histopathological evaluation in differentiating benign from premalignant lesions to ensure accurate diagnosis and optimal management.

Case Report

A 37-year-old widowed man presented with nodular lesions on the penile area that had been present for one year prior to presentation. Initially, the lesions were small and skin-colored, however they progressively enlarged and became erythematous over the past three months. The lesions were associated with intermittent pruritus and occasional easy bleeding. The patient also reported nodular lesions in the anal region that had appeared seven months prior to presentation. These lesions were initially small and gradually enlarged over several months. The patient denied pain, pruritus, or bleeding in the anal lesions

The patient had been diagnosed with Hodgkin lymphoma five years prior to presentation and had undergone two cycles of chemotherapy over a two-year period. A family history of malignancy was noted, as the patient's grandmother had leukemia. The patient denied any history of smoking. He had been married for eight years and divorced one year prior to presentation. He denied any history of extramarital sexual contact. The patient reported his first sexual intercourse occurred 13 years prior to presentation, and his last sexual contact with his wife was two years prior to presentation, involving genital–genital intercourse without condom use. There was no history of genital ulcers, genital warts, generalized erythematous rash, or multiple sexual partners in either the patient or his sexual partner.

Physical examination revealed right inguinal lymphadenopathy. Venereological examination of the penile shaft and pubic region demonstrated multiple erythematous papules with well-defined margins, irregular borders, and variable shapes and sizes as shown in Figure 1A. Examination of the perianal region demonstrated multiple skin-colored verrucous plaques with well-defined margins, irregular borders, and variable shapes and sizes as shown in Figure 1B. Anoscopic examination demonstrated intra-anal skin-colored verrucous plaques with well-defined margins, irregular borders, and variable shapes and sizes.

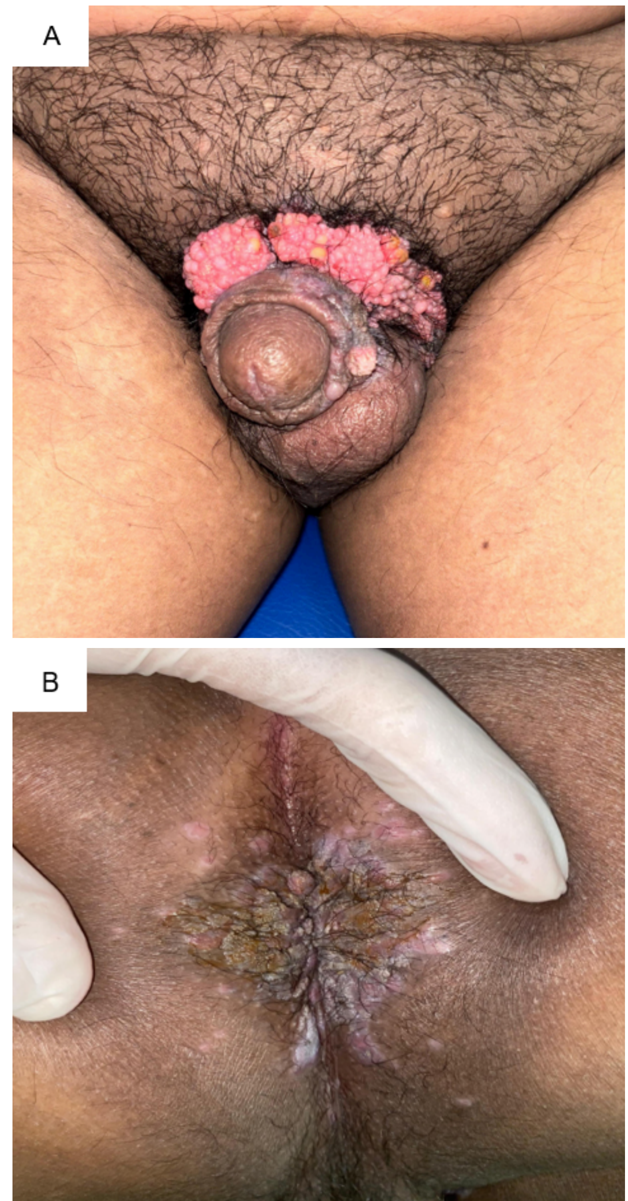

Figure 1. [A] Examination of penile shaft and pubic region revealed multiple erythematous papules with well-defined margins, irregular borders, and variable shapes and sizes. [B] Examination of the perianal region revealed multiple skin-colored verrucous plaques with well-defined margins, irregular borders, and variable shapes and sizes

Histopathological examination of a penile lesion obtained by shave biopsy revealed tissue fragments lined by stratified squamous epithelium with a papillomatous architectural pattern (Figure 2). The basement membrane was intact, and the atypical epithelial proliferation was confined to the full thickness of the epithelium without stromal invasion (Figure 3). The tumor consisted of proliferating polygonal keratinocytes with

round-to-oval pleomorphic nuclei, prominent nucleoli, eosinophilic cytoplasm, frequent atypical mitotic figures, and an increased nuclear-to-cytoplasmic (N:C) ratio as shown in Figure 4. Prominent intercellular bridges were identified. The underlying stroma was edematous and showed with mixed inflammatory cell infiltrates and dilated capillary blood vessels (hematoxylin–eosin staining). These histomorphological features were consistent with penile intraepithelial neoplasia. Given the presence of an increased N:C ratio and atypical mitoses, immunohistochemical staining for p16 as shown in Figure 5 was subsequently performed and demonstrated strong nuclear and cytoplasmic positivity in the atypical epithelial cells, supporting a diagnosis of HPV-associated penile intraepithelial neoplasia. HPV genotyping revealed positivity for HPV types 18 and 45.

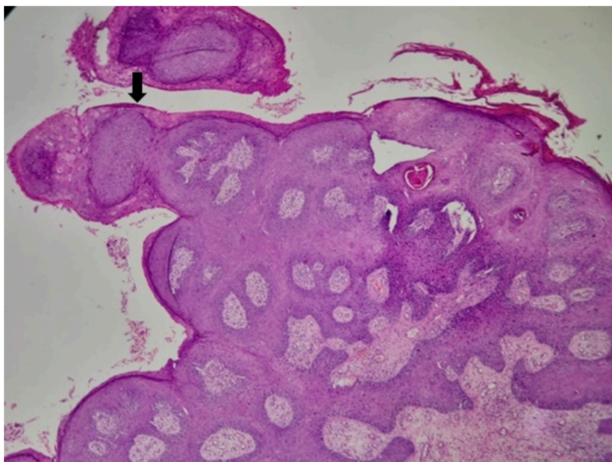

Figure 2. Stratified squamous epithelium exhibiting a papillary architectural pattern (H&E, ×100)

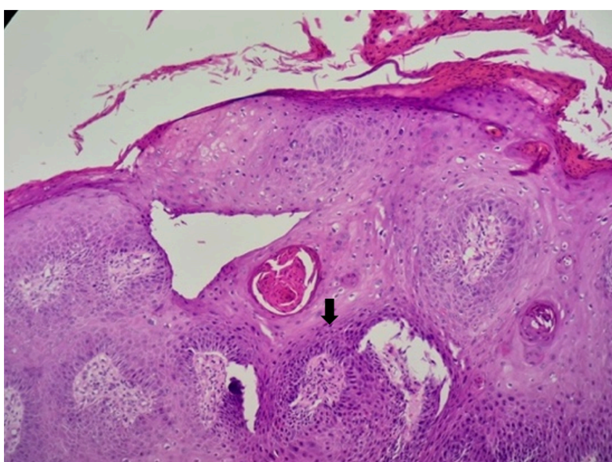

Figure 3. Preserved basement membrane without evidence of stromal invasion (H&E, ×100)

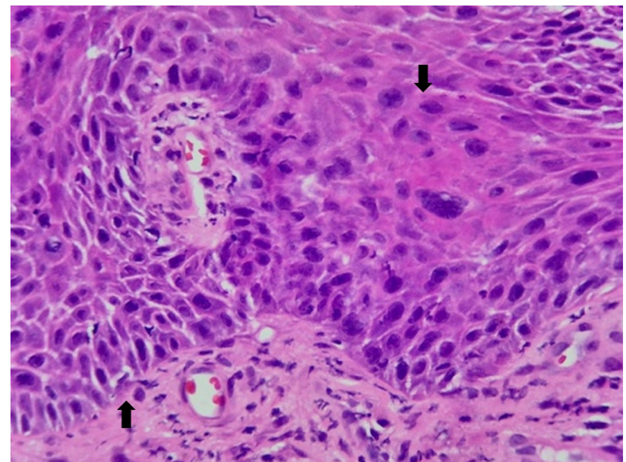

Figure 4. Proliferation of polygonal keratinocytes with round to oval pleomorphic nuclei, conspicuous nucleoli, and prominent intercellular bridges. An increased nuclear-to-cytoplasmic (N:C) and atypical mitotic are identified (H&E, ×400)

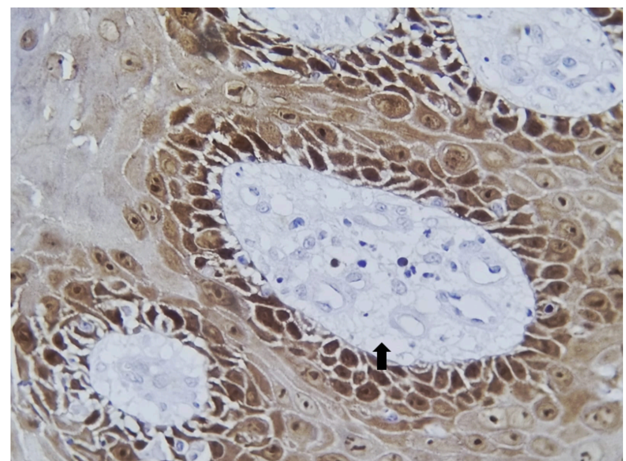

Figure 5. Diffuse nuclear and cytoplasmic P16 immunoreactivity in atypical epithelial cells (immunohistochemistry)

Histopathological examination of a perianal lesion obtained by shave biopsy revealed tissue fragments with a polypoid architectural pattern lined by hyperplastic stratified squamous epithelium (Figure 6). Koilocytotic cells characterized by pyknotic nuclei and perinuclear halos were identified as shown in Figure 7, consistent with condyloma acuminata. Based on the patient's history, physical examination findings, and supporting investigations, the final diagnosis was penile intraepithelial neoplasia and anal condyloma acuminata.

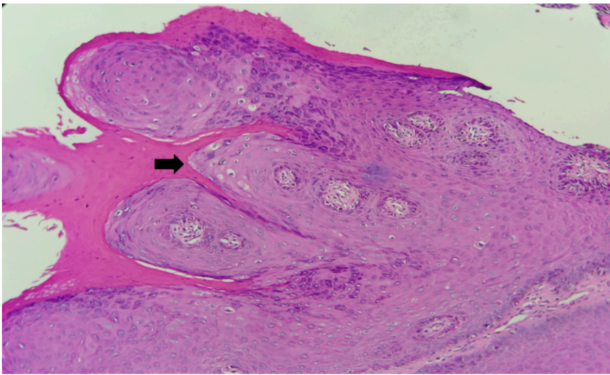

Figure 6. Polypoid lesion lined by complex, thickened squamous epithelium with papillomatous architecture (H&E, ×100)

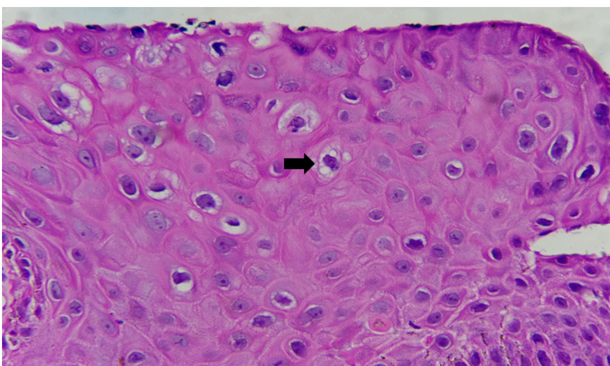

Figure 7. Koilocytotic cells characterized by pyknotic nuclei and perinuclear halos (H&E, ×400)

Following the establishment of the diagnosis, the patient was managed through a multidisciplinary approach involving the departments of dermatovenereology and urology, in coordination with the hematology–oncology team responsible for his Hodgkin lymphoma. In view of the diagnosis of HPV-associated penile intraepithelial neoplasia and its premalignant potential, the patient was referred to the urology department, where wide local excision of the penile lesions was planned as the definitive treatment. However, the patient had not yet undergone the procedure, as he remained hesitant to proceed given his recent chemotherapy for Hodgkin lymphoma and concerns regarding his general condition during the post-chemotherapy period. Ablative therapy was planned for the anal condyloma acuminata.

The patient was thoroughly counseled regarding the nature of the disease, its potential for malignant transformation, and the importance of completing the recommended treatment. In this case, histopathological examination through biopsy proved essential, as the possibility of malignancy could not be excluded on clinical grounds alone in anogenital lesions resembling condyloma acuminata, particularly in the context of the patient's immunocompromised status, history of Hodgkin lymphoma, and infection with high-risk HPV types 18 and 45.

Discussion

Human papillomavirus (HPV) infection is highly prevalent worldwide and affects individuals across all age groups. Its clinical manifestations are largely determined by the host immune response to virally infected cells [5]. HPV is a non-enveloped, double-stranded DNA virus belonging to the family Papillomaviridae [6]. Based on oncogenic potential, HPV is classified into high-risk and low-risk types. High-risk HPV types, such as HPV-16 and HPV-18, are associated with the development of squamous cell carcinoma, leading to cancers of the cervix, anus, penis, and oropharynx, as well as premalignant stages including cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VAIN), anal intraepithelial neoplasia (AIN), and penile intraepithelial neoplasia (PeIN). Low-risk HPV types, particularly HPV-6 and HPV-11, account for more than 90% of cases of condyloma acuminata [7].

Penile intraepithelial neoplasia (PeIN) is a premalignant lesion of penile squamous cell carcinoma and is considered a rare condition [8]. The average incidence of PeIN in the Netherlands is 0.47 per 100,000 population per year [3]. PeIN may arise due to HPV infection, most commonly HPV-16 as well as exposure to arsenic, excessive ultraviolet radiation, and cigarette smoking [1]. A report described eight patients with hematologic disorders or malignancies and the use of immunosuppressive agents for autoimmune diseases as additional risk factors for PeIN. According to the 2022 WHO classification, PeIN is categorized based on HPV association into HPV-related and non-HPV-related PeIN. HPV-related PeIN is more frequently observed in younger men [9-10]. HPV-associated PeIN has been reported to account for more than three-quarters of all PeIN cases [2]. In the present case, the patient was a 37-year-old man with a history of Hodgkin lymphoma and no history of smoking.

In immunocompromised individuals, reduced cellular immunity, particularly impaired $CD4^+$ T-cell and cytotoxic T-lymphocyte function, results in an inability to effectively eradicate HPV infection. This permits prolonged viral persistence and promotes epithelial cell transformation. Persistent infection enables the expression of viral

oncoproteins E6 and E7, which inactivate the tumor suppressor proteins p53 and retinoblastoma (Rb), disrupting cell cycle regulation and facilitating the accumulation of genetic mutations. Immunocompromised states are also associated with higher HPV viral loads, infection with multiple HPV genotypes, and a chronic inflammatory microenvironment that supports neoplastic progression [11].

Macroscopically, HPV-related PeIN exhibits heterogeneous clinical appearances, ranging from papules, macules, and flat plaques to slightly elevated lesions or nodules. Lesion coloration may vary from white and erythematous to darkly pigmented, and the borders are often well defined.[2] PeIN is typically asymptomatic; however, symptoms such as pain, bleeding, crusting, and pruritus may occur [12]. In this case, the patient complained of penile nodules accompanied by pruritus and occasional bleeding. Dermatological examination of the genital region revealed erythematous papules. Because the clinical morphology of PeIN is variable, it may resemble condyloma acuminata. Dermoscopic examination of penile lesions suspected of PeIN may aid in diagnosis. Dermoscopically, PeIN is characterized by orange, structureless areas and vascular patterns consisting predominantly of non-homogeneous dotted vessels and glomerular vessels [12]. In contrast, dermoscopic findings in condyloma acuminata typically include glomerular or dotted vascular patterns and characteristic knob-like and finger-like structures [2].

HPV-associated PeIN is most commonly classified into two subtypes: basaloid and warty (condylomatous), with the basaloid subtype being more prevalent. Basaloid PeIN is characterized by a population of relatively monomorphic, immature basaloid-appearing cells with a high nuclear-to-cytoplasmic (N:C) ratio, numerous mitotic figures, and prominent apoptosis[9] In differentiated (non-HPV-related) PeIN, p16 overexpression is usually absent, whereas in undifferentiated or HPV-driven PeIN, particularly the basaloid subtype p16 overexpression is typically present. Histopathological findings in this case were consistent with the basaloid subtype, and subsequent immunohistochemical staining demonstrated nuclear p16 positivity in tumor cells. Similar to invasive carcinoma, there is a strong correlation between p16 positivity and HPV infection, reported in approximately 84% of premalignant penile lesions [2,13]. HPV sequencing in this case revealed positivity for HPV types 18 and 45.

Condyloma acuminata is a sexually transmitted infection caused by HPV and is characterized by mucosal changes and cutaneous hyperplasia, predominantly in the anogenital region. HPV is transmitted through sexual contact, including genito-genital, oro-genital, and genito-anal contact. Microabrasions of the epithelial surface allow viral particles from an infected partner to enter the basal cell layer of an uninfected individual, which is the initial site of HPV infection. Following minor epithelial trauma, HPV particles gain access to basal epithelial cells [14]. Transmission may occur through contact with clinically apparent or subclinical lesions and/or genital secretions containing HPV. Less commonly, HPV transmission may occur through direct hand contact or indirectly via contaminated objects (fomites). The incubation period for condyloma acuminata ranges from two weeks to nine months, with an average of approximately three months [4].

The clinical forms of condyloma acuminata include condylomatous, keratotic, papular, and flat variants. Anogenital warts may be associated with symptoms such as pruritus, burning sensation, and pain. Patients with anal condyloma acuminata may be asymptomatic or present with painless papules, pruritus, discharge, or bleeding from the anus. It is not uncommon for multiple areas to be involved, with lesions extending into the anal canal or rectum [15]. In the present case, the patient reported anal warts without associated pruritus or pain, and venereological examination of the perianal and intra-anal regions revealed verrucous plaques.

Most cases of condyloma acuminata can be diagnosed based on history taking and clinical examination. When necessary, particularly in atypical or doubtful lesions, dermoscopic examination may be performed. Dermoscopy typically reveals glomerular or dotted vascular patterns and characteristic features such as a mosaic pattern in early flat lesions, as well as knob-like and finger-like structures in papillomatous lesions [4]. In this case, dermoscopy demonstrated finger-like features. Biopsy is not recommended as a routine diagnostic procedure for condyloma acuminata and is reserved for atypical lesions, lesions unresponsive to therapy, or when malignancy is suspected. Microscopically, condyloma acuminata is characterized by koilocytosis, defined as enlarged keratinocytes with perinuclear halos or vacuolization, often accompanied by hyperchromatic nuclei. Additional histopathological features include acanthosis, parakeratosis, and elongated rete ridges in the epidermis, as well as papillomatosis and chronic

inflammatory cell infiltrates in the dermis, all of which were consistent with the findings in this case.

Conclusion

Anogenital human papillomavirus (HPV) infection may manifest as benign lesions, such as condyloma acuminata, or as premalignant lesions, including penile intraepithelial neoplasia (PeIN). Establishing an accurate diagnosis requires a comprehensive approach, including histopathological confirmation, particularly in immunocompromised patients. This highlights the importance of heightened clinical vigilance and histopathological evaluation in such immunocompromised individuals, as clinical presentations may be more complex and atypical.

Conflict of Interest

The authors declare no conflict of interest.

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