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Case Report

Warty Squamous Cell Carcinoma of Anogenital Region: A Case Report in an HIV-positive Patient

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ABSTRACT

Venereal infections significantly contribute to the development of anogenital cancers, and Human papillomavirus (HPV) is the most common sexually transmitted disease worldwide. Warty squamous cell carcinoma is an extremely rare aggressive variant that generally occurs in the severely immunosuppressed at sites like the anogenital and genito-urethral regions. Though its etiology is thought to be multifactorial, 95% cases are attributed to HPV infection. Of the various subtypes, the high-risk HPV serotypes, particularly HPV16 and18, are the main risk factors for warty carcinoma.

We present the case of a 58-year-old male who came with complaints of a painful perineal lesion of three months duration. He is a known HIV-positive patient and has been on active antiretroviral therapy (HAART) regimen for the last 15 years. He was diagnosed with verrucous carcinoma of the perianal region five years ago for which an abdominoperineal resection was performed and now came with local tumor recurrence. Excision was done and histopathological evaluation showed an invasive carcinoma with papillomatosis, hyperkeratosis, and koilocytic atypia with brisk mitotic activity. Immunohistochemistry for p16 showed block positivity, confirming a diagnosis of HPV-associated warty squamous cell carcinoma. This case report highlights the relatively new variant of squamous cell carcinoma, its association with HPV, and the immunological implications of this virus in the development of squamous cell carcinoma. Preventive strategies to reduce such malignancies in the susceptible population have to be emphasized by creating awareness amongst the general public regarding the significance of HPV immunization and promoting the same in vulnerable groups.

Keywords: Warty, HIV, HPV, p16, Squamous cell carcinoma

INTRODUCTION

Anal malignancies are broadly divided into two types, one involving the anal canal and the other of the perianal skin. While anal squamous cell carcinoma accounts for only 4% of all distal large bowel cancers, perianal malignancies represent a smaller percentage of cases.[1,2] Of the several histological subtypes described, Warty carcinoma (WC) is especially uncommon and recent studies suggest the role of HPV in its pathogenesis.[3] HPV has a propensity to infect the basal keratinocytes producing altered cytokine expression and subsequent viral replication resulting in impaired host immune response.[4,5] There is also evidence for the rise in the incidence of malignancy in immunosuppressed hosts with HPV infection, which otherwise would have resolved in immunocompetent patients.[5] WC is a slow-growing tumor and hence often mistaken for a benign lesion. Arborizing papillomatosis, hyperkeratosis, parakeratosis, koilocytic atypia, multinucleation and nuclear pleomorphism are histological clues to the diagnosis of WC. p16 overexpression with block positivity has been found to be a surrogate marker for HPV and can be used for confirmation. Nevertheless, WC has a better prognosis compared to other variants of well-differentiated squamous cell carcinoma.

CASE REPORT

A 58-year-old male visited our surgery department with complaints of a painful perineal lesion of three months duration. It was a slow-growing tumor with an insidious onset. The patient's medical records showed an abdominoperineal resection performed five years ago for verrucous carcinoma and the present lesion seemed to be a local recurrence of the same. He also underwent multiple surgical interventions, which included an open cholecystectomy for gallbladder carcinoma and a colostomy in the years prior. He has been on anti-retroviral therapy for the past 15 years for HIV. The tumor was of dimensions 2 x 1.5 x 1 cm in the perianal region extending posteriorly to the intergluteal cleft for which a wide excision was done. Histopathological evaluation showed an invasive squamous cell carcinoma with marked hyperkeratosis, parakeratosis and papillomatosis with koilocytic atypia, multinucleation, large intracytoplasmic inclusions, and prominent nucleoli with scattered mitotic figures (Figure-1).

Since our carcinoma showed changes due to viral cytopathic effect, immunohistochemistry for p16 was done which showed block positivity and a final diagnosis of HPV-related warty squamous cell carcinoma was made (Figure-2). The patient was continuing with anti-viral HAART therapy, with no signs of recurrence during the two-year follow-up.

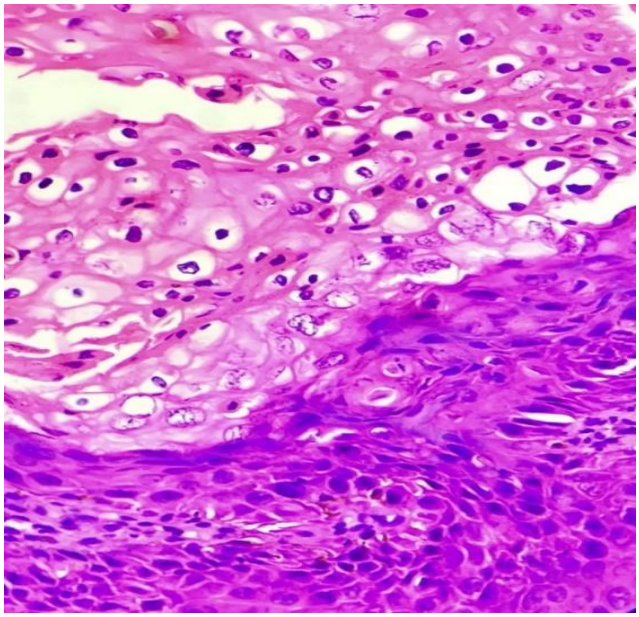

Figure-1: Invasive squamous cell carcinoma with hyperkeratosis and koilocytic atypia

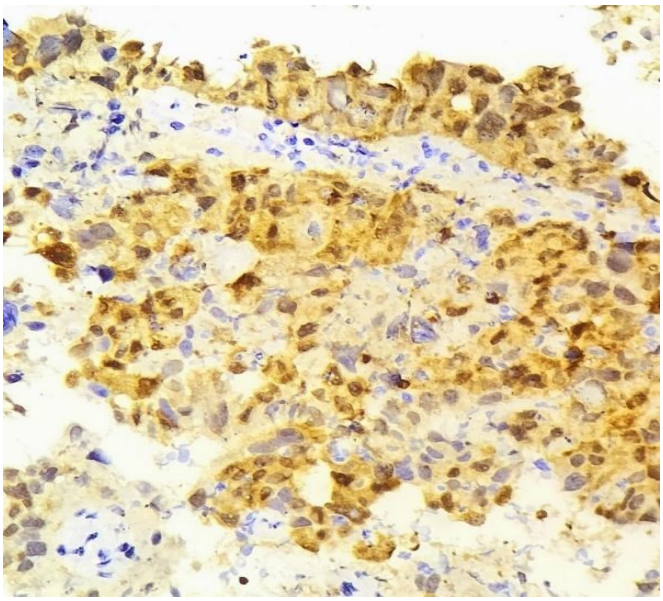

Figure-2: p16 immunohistochemistry shows block positivity

DISCUSSION

Anal squamous cell carcinomas (SCC) are relatively rare and account for approximately 4% of all neoplasms found in the distal large bowel.[1] Apart from conventional squamous cell carcinomas, various subtypes such as verrucous carcinoma, warty carcinoma and warty-basaloid types have been described. Warty carcinoma or condylomatous carcinoma is a recently described rare variant considered as a well-differentiated, low-grade verruciform tumor having two parts: condyloma and invasive SCC.[6] WC is commonly observed in the vulva, cervix and perianal region.[7] Warty squamous cell carcinoma has been linked to severe immunosuppression and is seen in immunocompromised states like HIV infection and organ transplant recipients. HIV-positive status is associated with an increased risk of developing HPV-associated anogenital malignancies and their precursor lesions and the increased risk is thought to be due to the impact of virus-secreted cytokines and chemokines to evade the host immune response by suppressing the E6 and E7 oncoproteins.[5]

Though its etiology is thought to be multifactorial, 95% of cases are attributed to HPV infection.[8] The viral oncoproteins E6 and E7 secreted by this oncogenic virus inhibit p53 and RB gene producing increased virion replication and the resultant viral cytopathic effect with koilocytic atypia and inclusion like nucleoli.[5] Low-risk HPV variants like type 6 and 11 express weaker versions of E6 and E7, hence genital warts caused by infection with low-risk subtypes of HPV are now considered to be precursor lesions of warty carcinoma.[6] The presence of high-risk HPV types has been observed in numerous cases

of cervical cancer, reinforcing the notion of its involvement in pathogenesis.[5,9] According to World Health Organization (WHO) data, only 0.3-1.2% of cases with HPV infection progress to malignancy and it is the host immunity that determines the progression of HPV-related precursors to full-fledged invasive carcinomas.[10] A study by Frisch et al found that HIV-infected individuals face a higher risk of developing anogenital carcinomas associated with HPV due to the release of inflammatory cytokines like transforming growth factor-β (TGF- β) and tumor necrosis factor-α (TNF-α).[3,4] The relative risk for developing anorectal carcinoma is 37 times greater among HIV-positive male homosexuals than that of the general population.[5] A two-year cumulative study conducted by Palefsky et al reported that HIV-positive men with low-grade lesions at the beginning of the study progressed to high-grade lesions within two years.[11] Transplant recipients on chronic immunosuppressive therapy have twice the risk of developing warts and malignancies when compared to the general population5. The increased risk in transplant recipients can be attributed to the use of calcineurin inhibitors that have an inhibitory effect on p53 and E-cadherin which promote skin carcinogenesis.[12] High levels of p53 and TGF-β, and low levels of phosphorylated mTOR with spindle cell morphology is the characteristic phenotype of SCC occurring in post-transplant patients. Other risk factors include smoking, a history of sexually transmitted diseases, and hematological abnormalities.[13] Patients typically present with a painful exophytic lesion associated with bleeding and ulceration.[8] Histopathology of these lesions show arborizing papillae with fibrovascular cores and koilocytic atypia, characteristic of HPV infection.[14] Due to similar histological presentation, WC is often misdiagnosed as condyloma acuminatum, verrucous carcinoma, and papillary squamous cell carcinoma as in our case. Since p16 is a surrogate marker for HPV, p16 immunohistochemistry with characteristic block positivity in WC can be used to differentiate between HPV-related WC and verrucous carcinoma. Though treatment depends on the characteristics of the tumor, the fundamental principle is complete excision with margin clearance to prevent local recurrence. The two-year follow-up of our case reported no signs of recurrence.

CONCLUSION

In conclusion, warty squamous cell carcinoma is a rare, aggressive subtype of invasive squamous cell carcinoma occurring commonly in the urethral and anogenital areas. Though there are many determinants contributing to its etiology, most of these lesions have a positive association with HPV infection. The idea behind this case report is to highlight the relatively new variant of squamous cell carcinoma, its association with HPV and the immunological implications. Immunosuppression plays a key role in the progression of benign HPV-infected lesions like condylomas to malignant variants. Arborising papillomatosis, hyperkeratosis and koilocytic atypia are histological clues for the diagnosis of warty carcinoma but they can often be misdiagnosed as benign warts like condylomas. The prognosis of WC is fairer when compared to other well-differentiated squamous cell carcinomas owing to its slow growth and low potential to metastasize. Because of the rising number of high-risk immunosuppressed populations, there is a proportionate increase in the incidence of these rare anogenital malignancies and their precursor lesions. The impact of the HPV vaccine needs to be emphasized in this regard and public health authorities should take effective strategies to expand the HPV immunization coverage to all target high-risk groups.

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