Large Anogenital Carcinoma Associated with Human Papilloma Viruses

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Abstract:

Anogenital condyloma/papilloma is the most common sexually transmitted disease (STD), and it is associated with human papilloma virus infection. However, anogenital papilloma/carcinoma greater than 10 cm in diameter is unusual. Here we report a case of unusually large anogenital verrucus carcinoma on both buttocks in a 33 year-old male associated with low risk and high risk HPV infections. Unusually large anogenital tumor is sometimes named as Buschke- Lowënstein tumor, also known as the anogenital subtype of verrucous carcinoma.
Introduction:

Anogenital papilloma/condyloma is an epidermal proliferation commonly associated with human papilloma virus, and it is the most common sexually transmitted diseases around the world \(^1\text{-}\text{3}\). Most of the anogenital papilloma/condylomas are small and associated with HPV type 6 and 11 with low to minimal neoplastic potential (low-risk HPV)\(^1\text{-}\text{4, 5}\). A small percentage of these skin lesions are associated with HPV type 16 and 18 with high risk neoplastic potential (high risk HPV), similar to cervical intraepithelial lesions \(^2\text{-}\text{6}\). Here we report a case of unusually large anogenital verrucous carcinomas on bilateral buttocks with HPV association.

Case Presentation:

A 33-year old African American male with high functioning intellectual disability presented to the emergency department with a complaint of rectal pain from an anal mass. This rectal pain was increasing in intensity for three month duration and aggravated by ambulation or exertion. Past medical history was unremarkable except for everyday tobacco use. Review of systems was positive for an anal wart, described as massive in size with pain, swelling, and discharge. Physical examination revealed an anxious appearing male, with malodorous discharge from an anal wart as large as a soccer ball in size protruding from the left and right buttocks. Bedside labs were draw, blood culture drawn, and wound culture and gram stain performed. Cefepime 2 grams IV and Levofloxacin 500mg IV were promptly begun in the emergency department. Initial impressions included infected anal wart and anal carcinoma. Four hours after admission, patient was admitted to surgical care for intervention and biopsy. Surgical procedure included resection of massive lesions of both buttocks with anal reconstruction. Three specimens were removed. From the left buttock, a large mass of 19x12x13 cm with skin and subcutaneous tissue was excised (Figure 1). From the right buttock, a mass of 12x7x9 cm with skin and subcutaneous tissue was excised. There was one additional lesion on the central perineal skin which was excised. Pathologically, all specimens showed similar features characterized by epidermal squamous proliferation in a papillary/verrucoïd pattern. Surface epithelium was keratinized and well differentiated with focally infiltrative border downward. There were frequent mitotic figures and nuclear pleomorphism within the tumor. The overall histopathologic features were consistent
with invasive verrucous squamous cell carcinoma. Chromogenic in-situ hybridization for human papilloma viruses (HPV) were performed at Integrated Oncology Lab, NY with appropriate controls. The tumor sections showed strong positive reactivity to low-risk HPV type 6/11, weakly positive for high risk HPV type 16/18. No reactivity to intermediate risk HPV type 31/33. Wound culture revealed *Escherichia Coli* and *Providencia Stuartii*, which were both sensitive to Ciprofloxacin. Patient was discharged home four days later and follow-up appointment one month later was scheduled but the patient did not show.

**Discussion:**

Anogenital verrucous carcinoma, also known as the Buschke- Lowënstein tumor, was first described by these two men in 1925. Verrucous carcinoma is a locally aggressive, slow-growing, well differentiated squamous cell carcinoma with minimal metastatic potential. Clinically it presents as an exophytic, cauliflower-like mass that occurs at sites of inflammation and chronic irritation. Cases have been reported of locally aggressive behavior that has penetrated into fascia, and bone. Anogenital subtype has the potential to ulcerate and form fistulae and sinuses; recurrence is common. With the incidence in the United States and worldwide unknown, reports show this tumor predominantly affects Caucasian males in their middle age and the immunocompromised. Mortality is due to local invasion rather than to metastatic spread. Anogenital verrucous carcinoma can be differentiated histologically from ordinary condyloma acuminata by its thicker stratum corneum and presence of endophytic downgrowth. Treatment of choice is considered wide surgical excision. Surgery alone has resulted in a disease-free status in 45.5% of patients. Controlled trials comparing treatments are lacking, but oral and topical chemotherapeutic modalities have been used as adjuvant to surgery. Topical therapy with 5-fluorouracil, podophyllin, or interferon has proven insufficient to control disease. Radiation therapy remains controversial. Recurrences can be successfully addressed with radical surgery with a cure rate of 61% versus only 25% with chemoradiotherapy with or without local excision.

Although causal role of HPV strains in carcinogenesis has not been directly supported; numerous studies showed that the E6 protein of HPV (6/11) subtypes binds tumor suppressor protein p53,
which leads to accelerated degradation of the p53 protein, inhibiting its transcription and tumor-suppressive function. The role of HPV in carcinogenesis is reinforced by the rare genetic disease Epidermodysplasia Verruciformis (EV). EV is an extremely rare, unique autosomal-recessive disorder that predisposes patients to body-wide HPV infection and cutaneous squamous cell carcinomas. EV patients develop flat warts and other skin lesions in the first decades of life, and these skin lesions degenerate to squamous cell carcinoma in the second and third decades of their lives. Detection of HPV-5 in EV cancers provided the scientific evidence of HPV in human carcinogenesis. Furthermore, EV patients carry genetic mutations of the EVER1 (TMC6) or EVER2 (TMC8) genes which are located adjacent to one another on chromosome 17, and EV patients showed various degrees of immunodeficiency.

The possibility of Epidermodysplasia Verruciformis has not been ruled out on this case due to inability to obtain detailed medical history, and unavailability of commercial diagnostic tests for EVER1 and EVER2 gene mutations.

**Conclusion:**

This case illustrates a rare opportunity to encounter a unique large anogenital tumor that has co-localization with the human papilloma viruses. Further research needs to determine exactly the viral pathogenesis, and to identify concrete risk factors.
Reference:


Figure legend:

Figure 1: Gross examination of surgically removed large buttock masses. The left buttock mass measured 19.0 X 13.0 X 12.0 cm, and the right 12.0 X 9.0 X 7.0 cm. A represents surface of the mass, and B is the cross section of the mass from the left.

Figure 2: Microscopic examination of the large buttock masses. A: The whole slide image of a tumor section; B: Surface of the tumor with papillary projections; C: Invasive downward growth pattern; D: Koilocytic effect of HPV with enlarged irregular nuclei and perinuclear clearing; E: Chromogenic in-situ hybridization for HPV (6/11) with strong nuclear staining signals; F: Chromogenic in-situ hybridization for HPV (16/18) with weak nuclear signals.