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Low Risk Is Different from No Risk: A Case Report of Low-Risk Subtype HPV-Related Perianal Squamous Cell Carcinoma

Dhruv Patel[1], Dillon Oliver Rogando[1*], Jordan Roy[2], Bjarne Faraon[1], Michael Polcino[2]

[1]The CUNY School of Medicine, New York, USA

[2]St. Barnabas Hospital, USA

[*]Corresponding author:

Dillon Oliver Rogando, BS,
The CUNY School of Medicine, 160 Convent Avenue, New York

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1. Abstract

There is a strong association between the incidence of perianal cancer and high-risk HPV subtypes, most notably HPV-16 [1]. In contrast, low-risk subtypes such as HPV-6 and HPV-11, are commonly implicated in the development of condyloma acuminatum or anogenital warts. While the association between high-risk HPV and perianal cancer has been well studied and characterized, there is limited evidence in the form of individualized case reports that report on the development of perianal cancer in the presence of low-risk HPV subtypes. In consequence, there are currently no established guidelines for annual perianal cancer screening in patients with either known low or high-risk HPV. However, there does exist screening for post-operative recurrence of perianal squamous cell carcinoma, which outlines treatment and screening recommendations. Due to the increased risk of developing perianal cancer from HPV infection, particularly the high-risk subtype, individualized screening should be emphasized. Overall, further work needs to be conducted on developing a generalized protocol that can potentially help decrease the incidence of perianal cancer in high-risk populations with either low-risk or high-risk HPV.

2. Keywords: General Surgery; Human Papilloma Virus; Oncology; Squamous Cell Carcinoma; Case Report

3. Introduction

Giant condyloma acuminatum or Buschke-Lowenstein tumor is a sexually transmitted disease caused by infection with *HumanPapillomaVirus*(HPV) subtypes 6 and 11 [1]. Infection with HPV manifests as hypertrophy of the infected tissue characterized by thick, discrete lesions commonly referred to as warts [2]. HPV possesses viral oncoproteins, E6 and E7, that drive cells toward oncogenesis. E6 targets p53, an important growth suppressor, while E7 targets pRB[3]. The dysregulation of these growth suppressor proteins leads to subsequentially dysregulated proliferation of infected cells.

According to the Center for Disease Control and Prevention (CDC)'s latest report on HPV and its epidemiology, the prevalence of any of the HPV genital subtypes was 45.2% among US men aged 18 through 59 years and 39.9% among US women in the same age range [4]. HPV is responsible for mucocutaneous and anogenital lesions that can progress to cancer and is implicated in the pathogenesis of 91% of cervical and anal cancers, 69% of vulvar cancers, 75% of vaginal cancers, 63% of penile cancers, and 70% of oropharyngeal cancers [4]. There are an estimated 27,000 new cases of anal cancer each year attributable to HPV- associated infection [5]. Risk factors include immunosuppression and a history of venereal disease. HIV-positive men who have a CD4 cell count of ≤ 200 cells/mm3 have a three-fold increase in the transformation rate of normal epithelium to anal squamous intraepithelial lesions [6].

It is important to note that amidst the innumerable HPV subtypes, within the scope of this article we focus on those that have been deemed to be carcinogenic or probably carcinogenic (HPV subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). According to a meta-analysis aimed at identifying the relationship between these high-risk HPV subtypes and the development of anal cancers, HPV-16 has been shown to be the most carcinogenic subtype. Among all identified anal cancers, the HPV-16 subtype

was present in over 85% of cases [7]. With regards to perianal skin cancers specifically, there is a paucity of data, however, the HPV-16 subtype has also been suggested to be the most prevalent and subsequently carcinogenic subtype. An analysis by Bjørge et al [8] of a Finnish and Norwegian patient registry reported over half of perianal cancers, histologically identified as squamous cell carcinoma, to be seropositive for HPV 16, 18, 33, and 73 with a greater number of individuals being seropositive for the HPV- 16 subtype. Moreover, infection with the HPV-16 subtype carries the greatest carcinogenic potential in the development of anal and perianal cancers.

The anal canal, which is about 4 to 5 cm long, begins from the lower rectal mucosa and includes the area where rectal mucosa transitions to the modified squamous epithelium of the anal canal, along with the dentate line. It extends to the point where the skin becomes keratinized at the anal verge. In essence, anal canal cancer encompasses any abnormality that cannot be fully observed through external examination alone. Perianal cancer encompasses lesions visible during external examination, requiring the separation of the buttocks to a distance of up to 5 cm from the anus. Lesions located beyond this 5 cm radius are classified as skin cancers [9].

Treatment with excision alone with adequate margins of 1 cm is only reserved for well-differentiated T1 N0 M0 perianal tumors [10]. After excision with negative margins, monitoring for 5 years with digital rectal exam, inguinal exam, andanoscopy every 3-6 months is recommended [10]. Positive margins require re-excision and Chemoradiotherapy (CRT). All other perianal tumors T2 or greater +/- poorly differentiated T1 N0 and tumors of the anal canal require CRT with mitomycin and 5-fluorouracil [9].

Although HPV subtypes 6 and 11 are considered low risk as they tend to cause warts and not cancer [11], we present a case report of invasive perianal squamous cell carcinoma arising from giant condyloma acuminatum positive for HPV 6 and 11.

4. Case Presentation

The patient is a 40-year-old male with a medical history of hypertension as well as congenital HIV, controlled on HAART, who presented with a chief complaint of pain at the site of a large fungating perianal mass. An initial physical exam revealed frank pus draining from the mass with leukocytosis of 25.7. A CT scan was completed to further characterize the mass as well as help with metastatic workup Figure 1. No signs of metastasis were seen in the chest, abdomen, or pelvis. The patient said this mass was initially much smaller and was resected once before but it had recurred. The patient was started on IV antibiotics and, once stable, was taken to the OR for his index operation–an exam under anesthesia with tissue biopsy as well as laparoscopic descending loop colostomy creation. This helped divert stool away from the mass and the surgical team now had a diagnosis for the mass: Squamous Cell Carcinoma (SCC) with positive HPV 6 and 11 markers.

After the index operation, the decision was made to perform a complete colonoscopy through both the proximal and distal loops of the colostomy. This would not only inform of any other masses in the colon, but would also help elucidate if the mass involved any part of the anus or rectum. If it did, this would change the diagnosis from a perianal SCC to an anal canal SCC, which would benefit more from chemotherapy and radiation (Nigro protocol) rather than resection [12]. The colonoscopy was negative for any other masses and did not show the mass invading the anal canal.

The patient was then nutritionally optimized to allow better healing of his future excision site. The patient was finally taken to the operating room for wide local excision of the tumor. The patient was placed in prone jackknife position and a skin incision was made around the tumor, which was then dissected down through subcutaneous tissue and fat to the gluteus muscle. Care was taken to avoid and control bleeding while continuing resection. Finally, once the mass was excised, anoplasty was done to secure the anus to the sphincter complex with sutures (Fig. 2A and 2B). The levator muscles were left intact, and an immediate plastic surgery reconstruction was then done, which the patient tolerated well.

The final pathology diagnosed the specimen as an 18x17x5cm invasive squamous cell carcinoma with moderate differentiation and with no lymphovascular invasion identified. The tumor was diagnosed as T4. The patient after surgery did well and was discharged on post op day 9.

5. Ethics Statement

This case report was approved by the Institutional Review Board of St. Barnabas Hospital.The requirement for informed consent was obtained.

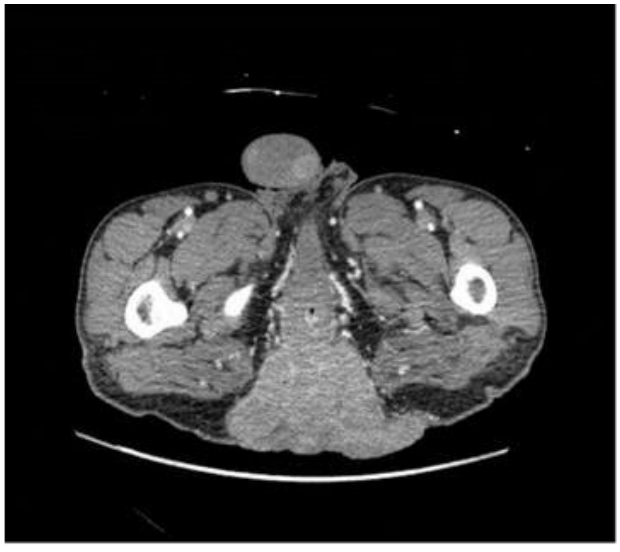
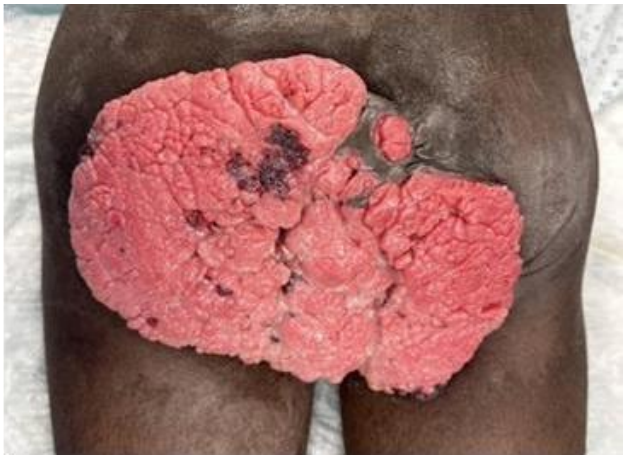


Figure 1: Abdomen and Pelvis demonstrating a large fungating perianal mass abutting anus.



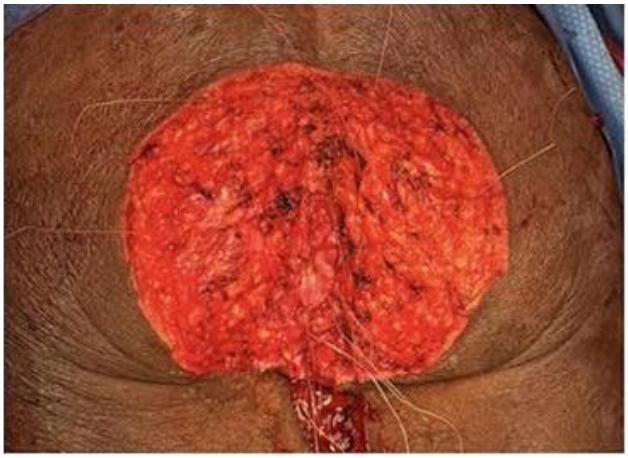


Figure (2A&B): Pre-operative and post-operative photograph of wide local excision of perianal SCC tumor with preservation of the anus.

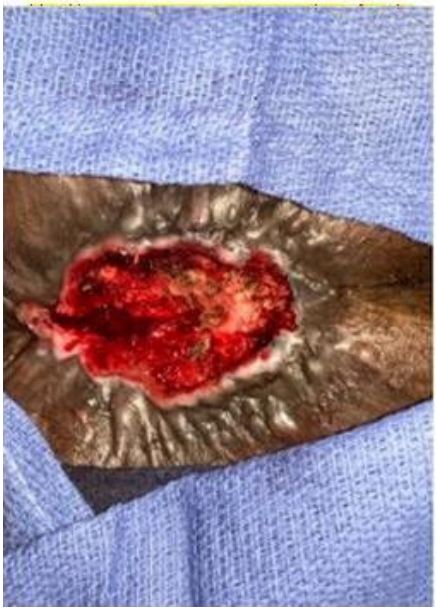


Figure 3:30 days post-operative photograph of wide local excision of perianal SCC tumor with preservation of the anus.

6. Discussion

In this report, we present a case of T4 invasive perianal squamous cell carcinoma, caused by low-risk HPV-types 6 and 11. It is estimated that 90% of cervical and anal cancers are due to infection from high-risk HPV-types 16 and 18 [13]. On the other hand, developing anal or perianal cancer from low-risk HPV subtypes is quite rare. One study, analyzing etiology in a population of 81 cases of anal cancer, found that the absolute frequency of HPV 6 and HPV 11, respectively, detected in anal cancer was

less than five. Comparatively, the absolute frequency of HPV 16 detected in single infection and multiple infections in anal cancer was greater than 45 [14]. Another study found an association between mono infection by HPV-6 and progression to High- Grade Squamous Intraepithelial Lesion (HSIL) [15]. Furthermore, individual case reports have reported chronic mono infection by HPV genotypes 6, 11, 42, 44, or 70 to be the cause of a small number of perianal cancers [16]. Overall, research has shown that while high-risk HPV has a significantly stronger association with perianal and anal canal cancer, there still may be a potential relationship with low-risk HPV subtypes as well.

Currently, there are no uniform established guidelines for annual perianal cancer screening in patients with known low or high- risk HPV. However, the International Anal Neoplasia Society has recommended that individuals aged =45 years with a history of cervical/vaginal HSIL or cancer, perianal warts, persistent (>1 year) cervical HPV 16, or autoimmune conditions could be considered for screening with high-resolution anoscopy, anal cytology, high-risk human papillomavirus testing, and hrHPV-cytology co-testing [17]. There does, however, exist screening for post-operative recurrence of anal squamous cell carcinoma. This algorithm recommends surveillance for 5 years. For 5 years, digital rectal exam and inguinal node exam every 3 to 6 months is recommended. For 3 years, anoscopy is recommended every 6 to 12 months. CT scans of the chest, abdomen, and pelvis are recommended every 12 months for 3 years [9]. Furthermore, this algorithm recommends treatment with groin dissection in those with positive lymph nodes and salvage abdominoperineal resection with or without extended resection in those with locoregional cancer recurrence. For patients with metastatic recurrence, systemic therapy is advised.

HPV prevalence is highest in young adults, with prevalence increasing with age from 14 to 24 years and peaking between the ages of 25 and 29. Furthermore, Hispanic Black adults have the highest prevalence of genital HPV, while non-Hispanic Asian adults have the lowest. On the other hand, white men and women have a higher incidence of HPV-associated cancers while Asian/ Pacific Islander men and women have the lowest [18-19]. Specific populations at increased risk for developing HPV-related anal or perianal cancer include men who have sex with men, HIV-positive individuals, women with a history of cervical, vulvar, or vaginal cancer, and elderly people [20]. Therefore, given the increased risk of developing cervical and anal cancers from infection with HPV, particularly the high-risk subtype, individualized screening should

be emphasized in patient populations that are stratified to be "high risk" based on prior research. Given the lack of standardized guidelines for anorectal cancer screening in HPV-positive patients, further work needs to be conducted on developing a generalized screening protocol that can potentially help decrease morbidity and mortality of cancer in high-risk populations. Currently, the standard of care for early-stage perianal cancer is wide Local Excision (LE). Local excision is preferred due to the ability to preserve anal function in contrast to radical resection, which carries an additional risk for urinary and erectile dysfunction. Generally, the practice of local excision is reserved for lesions that are stage T2 or lesser, without any evidence of nodal involvement or metastases. One study examining the effectiveness of LE for early-stage perianal cancer found a 5-year disease free survival rate of approximately 71% which improved to 83% with adjuvant chemoradiotherapy. Despite this 5-year disease free survival rate, LE is still inferior with regard to overall survival as compared to radical resection. Therefore, careful evaluation of tumor invasion is necessary to determine the appropriateness of LE and patients should undergo routine follow-up to monitor for recurrence. As suggested by Weitfeldt, an anorectal and nodal examination should be performed every 3 months for two years following surgery and subsequently biannually until year 5. In the setting of advanced tumors, particularly T3 and T4 lesions, treatment with chemotherapy, External Beam Radiation Therapy (ERBT), and interstitial implant therapy have been demonstrated to be highly effective in obtaining locoregional control. In our patient, despite his advanced T4 lesion, local excision of the tumor proved to be effective. Strict adherence to screening for recurrence was emphasized due to the inherent risk of recurrence of the wide local excision technique.

As our case presentation demonstrated, although the relationship between low-risk HPV and perianal cancer is rare, it can still be present in isolated cases. Like in our patient, these cases may need management that is urgent. Therefore, not having a standardized protocol to guide initial treatment can delay action and potentially lead to poor health outcomes, including associated morbidity and mortality. In our case, the treatment was individualized to the patient's symptoms and intraoperative findings, which led to positive post-discharge findings. He is currently clinically stable and improving, has gained weight, and had his ostomy reversed. This experience also vouches for incorporation of individualized management in addition to following a standardized protocol. Overall, we hope that our case and suggestions for further research to be conducted lays a foundation for guidelines to be developed that will help direct screening and treatment for HPV-associated anal cancer and perianal cancer.

6. Author Contributions

6.1. Conceptualization:

All authors; Formal analysis: Dhruv Patel and Dillon Rogando; Investigation: all authors; Methodology: Dhruv Patel and Dillon Rogando; Project administration: all authors; Supervision: Jordan Roy and Michale Polcino; Validation: Jordan Roy and Michael Polcino; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

6.2. Conflicts of Interest:

The Authors have no conflict of interests to declare.

6.3. Funding:

Not applicable.

6.4. Acknowledgements:

Not applicable.

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