



ORIGINAL RESEARCH PAPER

Oncology/Radiotherapy

CLEAR CELL VARIANT OF SQUAMOUS CELL CARCINOMA PENIS – A CASE REPORT

KEY WORDS: clear cell carcinoma, penile tumors, human papilloma virus

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ABSTRACT

Carcinoma penis is a rare malignancy in males. The World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs classifies squamous cell carcinoma of the penis into human papillomavirus (HPV) and non HPV related. Among the HPV-related Squamous cell carcinomas of the penis, clear cell variant is a rare. Here we report a case of clear cell variant of squamous cell carcinoma of penis with bilateral inguinal lymph node metastasis. We have treated this patient with radical surgery, wide excision and bilateral inguinal lymph node dissection followed by post operative chemo radiation. But during radiation itself the disease progressed, with rapid recurrence of inguinal lymph node metastasis, finally end up with palliative chemotherapy. Clear cell carcinoma is an aggressive form of cancer, with frequent metastasis to the inguinal lymph nodes, as seen in this case. Immunohistochemistry examination P16 was absent. So it is considered as clear cell variant of squamous cell carcinoma. Clinical experience with penile carcinoma is limited because of their rarity.

INTRODUCTION

Clear cell carcinoma penis is one of the rarest malignancy in males. The incidence of penile cancers are only 1% of all cancers in males. Incidence is more in developing countries like Asia, Africa, and South America, when compared to Western Countries.^{1,2} In India, the incidence also varies in rural and urban areas as 3 cases per one lakh men in rural areas and 0.7 to 2.3 cases per one lakh men in urban areas.³

Incidence increases with age, usually occurs in sixth and seventh decades.^{2,4} The important risk factors in penile cancer are HPV infection and phimosis.^{2,5,6} Poor hygiene, smegma, immunosuppression are other associated risk factors. Among the HPV infection HPV 16, and 18 subtypes are associated with penile cancer.^{7,8} Chronic smoking is also a risk factor for increased incidence of penile cancers.⁹

The commonest type of penile cancer is squamous cell carcinoma, constitutes about 95% of tumors of penis.¹⁰ According to WHO classification of squamous cell carcinoma of penis is classified as HPV related and HPV independent type.¹¹ HPV related penile cancer are pathologically classified as 4 types. They are Warty type, Warty Basaloid type, Papillary basaloid, Lymphoepithelioma like carcinoma and Clear cell carcinoma (Table I). Among these, clear cell carcinoma the rarest type which was first reported in 2004.^{10,12} Spread is mostly through lymphatics, superficial and deep inguinal lymph nodes are involved in 50% of patients with penile cancers.^{11,13} Distant metastasis to lungs, seen 1-10%.¹³

Table 1: 2016 WHO pathological classification of penile squamous cell carcinoma according to HPV presence

Non HPV related	HPV related	Others
Squamous cell carcinoma Usual	Basaloid	Mixed HPV/ non HPV
Pseudohyperplastic	Papillary basaloid	Unclassified
Pseudoglandular	Warty	
Verrucous	Warty basaloid	
Pure	Clear cell	
Cuniculatum	Lymphoepithelioma like	
Papillary NOS		
Adenosquamous		
Sarcomatoid		
Mixed		

CASE PRESENTATION

51 year old male with no comorbidities, presented with ulceroproliferative lesion on the penile shaft of 9 months duration and bilateral inguinal swellings for 2 months duration. There was associated difficulty in micturition and dysuria. On physical examination there was a 6*4*3 cm ulcerative lesion involving the entire glans penis with bilaterally enlarged inguinal lymph nodes. Basic laboratory investigations including complete blood count, renal function test, liver function tests, random blood sugar were normal.

RADIOLOGICAL FINDINGS

Contrast enhancing CT scan abdomen and pelvis taken, which shows well lobulated heterogeneous mass lesion with minimal enhancement noted involving glans penis of size 6.5*4.5*4.7 cm with multiple enlarged bilateral inguinal lymph nodes. PET CT scan taken which does not show any distant metastases.

CLINICAL DIAGNOSIS Carcinoma penis with lymph node metastasis

DIFFERENTIAL DIAGNOSIS

1. Sebaceous carcinoma
2. Skin adnexal tumors
3. Metastatic renal cell carcinoma

PATHOLOGICAL DISCUSSION

Sections show an infiltrative neoplasm composed of cells arranged in nests and sheets. Individual cells have moderate to abundant pale eosinophilic vacuolated cytoplasm and pleomorphic vesicular nuclei, with prominent nucleoli. These clear cells are diagnostic of clear cell carcinoma (figure 2). Mitosis seen.

Immunohistochemistry examination p 16 was absent (figure 5). Areas of necrosis seen. Lymphovascular emboli and perineural invasion seen. Tumor is infiltrating urethra, corpora cavernosum and corpus spongiosum. Sections from right inguinal lymph node group show 5 lymph nodes, 4 of which show metastatic deposits with extranodal extension. Sections from left inguinal lymph node group show 5 lymph nodes, all of them show metastatic deposits with extra nodal extension.



Fig 1: CECT image showing enhancing mass lesion involving glans and enlarged bilateral inguinal lymph nodes

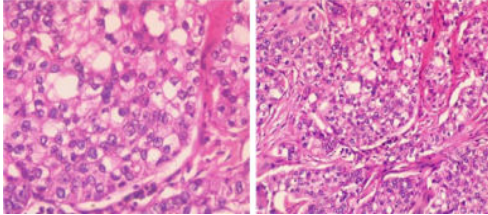


Fig 2: Histopathology image showing clear cells, 40X magnification

Fig 3: 10X magnification

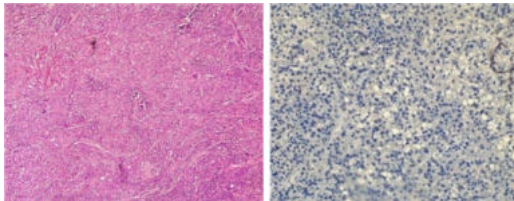


Fig.4: 4X magnification

Fig.5: IHC: p16 – negative

DISCUSSION ON MANAGEMENT

Clear cell carcinoma is an aggressive form of cancer with early metastases to regional lymph nodes, as seen in our case. Lymphovascular emboli and perineural invasion seen in our case also in favour of clear cell carcinoma¹². In pure clear cell carcinoma p16 will be positive, but in our case p16 is negative.⁸ So it is considered as clear cell variant of squamous cell carcinoma. Clear cell carcinomas are usually arising from sweat glands and most of the sweat gland carcinomas are large ulcerated tumors. To differentiate by immunohistochemistry, where Muc-1, CEA, EMA are helpful in establishing the correct diagnosis.¹⁴ Muc-1 is negative in squamous cell carcinoma. CEA and EMA are markers of sweat gland tumors.^{15,16} Our patient is treated with wide local excision with bilateral inguinal lymph node dissection. On pathological examination 4 out of 5 lymph nodes on right and 5 out of 5 lymph nodes on left inguinal region are showing metastatic deposits with extracapsular spread also. These features show the aggressive nature of the disease. We have treated this patient with radical surgery, wide excision and bilateral inguinal lymph node dissection followed by post operative chemo radiation. But during radiation itself the disease progressed, with rapid recurrence of inguinal lymph node metastasis, finally end up with palliative chemotherapy. These aggressive treatments, like surgery, chemotherapy, and radiation did not seem to improve the natural course of the disease.¹⁷ Clinical experience with different treatment modalities are very less because this is a rare type of cancer.

FINAL DIAGNOSIS

Clear cell variant of squamous cell carcinoma penis

REFERENCES

1. Siegel R, Ward E, Brawley O, Jemal Cancer Statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011;61:212-236
2. Pow-Sang MR, Ferreira U, Pow Sang JM, Nardi AC, Destefano V. Epidemiology and natural history of penile cancer. *Urology.* 2010;76:S2-6
3. Bleeker MC, Heideman DA, Snijders PJ, Horenblas S, Dillner J, Meijer CJ.

- Penile cancer: Epidemiology, Pathogenesis and prevention. *World J Urol* 2009;27(2):141
4. Hernandez BY, Barnhdtz- Sloan J, German R. Burden of Invasive squamous cell carcinoma of the penis in the United states 1998-2003. *Cancer* 2008;113:2883-2891.
5. Morrison B, Risk factors and Prevalance of Penile cancer. *West Indian Med J* 2018;63:559-560
6. Dillner J, Van Krogh G, Horenblas S, Meijer CJ. Etiology of squamous cell Carcinoma of the penis. *Scand J Urol Nephrol suppl.* 2000: 189-193.
7. Singh AK, Pandey BB, Jangir N, Human papilloma virus associated Carcinoma penis: A comparative study for histopathological correlation and outcome analysis. *Int Surg J* 2019;6:2813-2817.
8. Bansal A, Singh MP, Rai B. Human papilloma virus associated cancers: A growing global problem. *Int J of Applied and Basic Medical Research* 2016;6(2):84
9. Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer. Importance of Circumcision, human papilloma virus and Smoking in situ and invasive disease. *Int J Cancer* 2005;116:606-616.
10. Burt LM, Shrieve DC, Tward JD, Stage Presentation, case patterns, and treatment outcomes for squamous cell carcinoma of the penis. *Int J Radiation Oncology Biol Phys.* 2014;88:94-100.
11. Moch H, Cubilla AL, Humphrey PA et al. The 2016 WHO classification of tumors the ordinary system and male genital organs- Part A: Renal, penile and testicular tumors. *Euro Urol* 2016;70:93-105.
12. Liegl B and Regauer S. Penile clear cell carcinoma: A report of 5 cases of a distinct entity. *Am J Surg Pathol* 2004;28:1513-1517
13. Mannweiler S, Sygulla S, Tsybrovskyy O et al. Clear Cell differentiation and lymph node invasion, but not the revised TNM Classification, predict lymph node metastasis in PT, Penile cancer: A clinicopathologic study of 76 patients from a low incidence area. *Urol Oncol* 2013;31:1378-1385.
14. Yoshii N, Kitajima S, Yonezawa S, et al. Expression of mucin core protein in extramammary paget disease. *Pathol Int.* 2002;52:390-399.
15. Wong T-Y, Suster S, Nogita T, et al. Clear cell eccrine carcinoma of the skin. *Cancer.* 1993;73:1631-1643.
16. Santa Cruz DJ. Sweat gland carcinomas: a comprehensive review. *Semin Diagn Pathol.* 1987;4:38-74.
17. Sanchez DF, Rodriguez IM, Piris A et al. An HPV related variant of squamous cell carcinoma. *Am J Surg Pathol* 2016;40:917-922.