

Histological images of precancerous lesions and penile cancer *in situ*

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KEY WORDS

penile squamous cell carcinoma ▶ penile
intraepithelial neoplasia ▶ precancerous lesions ▶
HPV ▶ Bowen's disease

ABSTRACT

The majority of malignant tumours of penis are squamous cell carcinomas (SCC) and they chiefly occur in the squamous epithelium of the glans, coronal sulcus and foreskin. SCC develops via human papillomavirus (HPV) – associated precursor lesions (penile intraepithelial neoplasia; PIN) that are graded I-III depending on the epithelial thickness occupied by transformed basaloid cells. These cells vary in size and shape, with the nuclei being pleomorphic, hyperchromatic; they lose polarity. In grade I, PIN occupies the lower one third, in grade II the lower two thirds, and in grade III full epithelial thickness. PIN III is in other words called Bowen's atypia or *in situ* SCC. HPV is present in a subset of penile SCC, with HPV 16 being the most frequent type. HPV DNA is preferentially found in cancers with either basaloid and/or verrucous character, and is rarely correlated with typical keratinizing SCC. Penile intraepithelial neoplasia is consistently HPV DNA positive in 70-100% of cases. The HPV negative invasive cancers do not arise from the HPV positive PIN, but from unrecognized HPV-negative precursor lesions.

INTRODUCTION

Penile cancer develops in the mucous membrane of the glans, coronal sulcus and foreskin. Squamous cell carcinomas are predominant among neoplasms developing in those areas. Conditions favouring the development of penile cancer may include phimosis, chronic inflammatory lesions, especially *lichen sclerosus*, papillomas and lesions being a result of ultraviolet radiation and cigarette smoking. Moreover, it is thought that lack of circumcision is a factor increasing the risk of this cancer. Infection with human papillomavirus (HPV) is a significant factor associated with transformation of stratified squamous epithelium into cancer. Koilocytosis which may be detected in cells during cytological or histological examination is a morphological determinant of HPV infection. The characteristic features of a cell with koilocytosis include enlarged nucleus, wrinkled cell membrane, perinuclear halo and concomitant dyskeratosis and acantholysis of keratinocytes. Molecular tests, *in situ* hybridization or PCR are used to confirm HPV infection. Positive result of HPV DNA genetic testing, being a precursor of neoplastic transformation, is seen in 70% to 100% cases of penile intraepithelial neoplasia (PIN).

PRECANCEROUS LESIONS

Precancerous lesions for penile squamous cell carcinoma include HPV infection, intraepithelial neoplasia, Bowenoid papulosis and Bowen's disease, as well as Paget's disease.

HPV INFECTION AND INTRAEPITHELIAL NEOPLASIA – HPV, PIN [1]

About 30 types of human papillomaviruses are sexually transmitted. Due to the risk of cancer in stratified squamous epithelium which is associated with them they have been divided into types of low or high risk of neoplastic transformation. Clinical changes in the form of prominent verrucous growths called *condylomata acuminata* coexisting with infection caused by types 6 and 11 are associated with a low risk of malignant transformation. However, types 16 and 18, characterised by high risk of cancer, are detected in subclinical infections of the mucous membrane. Penile intraepithelial neoplasia (PIN) with coexisting HPV infection is a morphological precancerous lesion for penile squamous cell carcinoma. Depending on the extent of involvement it is classified into three grades (I, II, III). The main classification criterion is the number of epithelial layers infiltrated by abnormal cells which are characterised by polymorphy of shapes and sizes, large and hyperchromatic nuclei and loss of polarity. PIN I is diagnosed when the changes are present in the lower one third of full epithelial thickness, PIN II – two thirds and in PIN III the changes occupy full epithelial thickness. Other names for PIN III include Bowen's atypia, preinvasive cancer. Intraepithelial neoplasia may be accompanied by benign wart-like growths, which is associated with coexistence of both types of HPV infection, namely of low and high risk.

BOWENOID PAPULOSIS AND BOWEN'S DISEASE

Bowenoid papulosis is a clinical change present in young men (mean age is 18 years) which is sexually transmitted. Its morphological picture is similar to PIN III. HPV 16 is the most frequently detected type of HPV; however, 18 and/or 33-35 types may also be present. Bowenoid papulosis is a clinically benign lesion and mainly transient, it may regress spontaneously. It is treated with saving therapies. Following surgical treatment it may become calcified. Nonetheless, some cases transform into Bowen's disease, intraepithelial neoplasia III, namely precancerous lesions and sometimes invasive cancer.

From a clinical point of view it is not possible to determine in which patients HPV infection will result in progression from PIN III to invasive cancer. The age below 40 and immunosuppression in younger patients are factors identifying a group of patients with precancerous lesions.

PAGET'S DISEASE

Paget's disease is an intraepithelial form of adenocarcinoma primarily developing in the epithelium or spreading from skin tumours. The microscopic picture shows characteristic foci of large cells with light or vacuolised cytoplasm proliferating through the whole epithelial thickness. It is important to notice that the so called pagetoid spread of cells in the epithelium should be differentiated with transitional cell cancer, Bowen's disease and melanoma. Additional testing, such as positive mu-

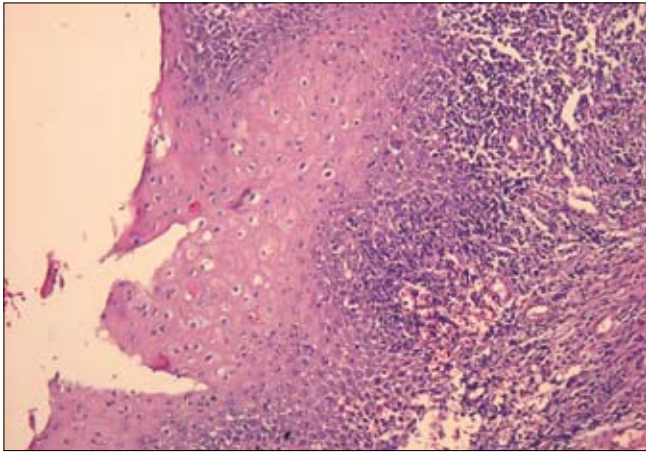


Fig. 1A. HPV infection in penile mucosa (H&E), x 40.

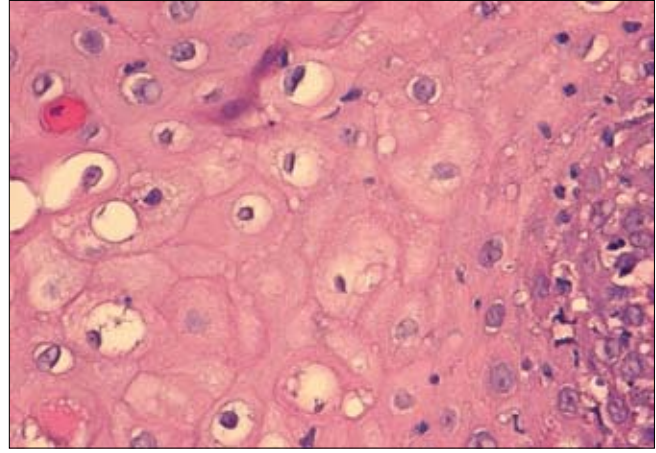


Fig. 1B. Chronic infection of the penis with HPV (H&E), x 40.

cus staining and immunohistochemical expression of carcinoembryonic antigen (CEA), low molecular weight keratin and HMB45 are useful diagnostic tools.

SQUAMOUS CELL CARCINOMA *IN SITU* AND INVASIVE CANCER

Squamous cell carcinoma *in situ* corresponds to the morphological image of intraepithelial neoplasia of high intensity, PIN III. Its variant is preinvasive Bowen's cancer with the presence of large pleomorphic cells called Bowen's cells.

The diameter of invasive penile squamous cell carcinoma is 3 to 4 cm. Macroscopically it has three forms: superficial and horizontal infiltration with superficial invasion, vertical growth with deep invasion and multifocal lesions. The microscopic picture shows different fields including well-differentiated cells with a different extent of keratinization and poorly differentiated, spindle-shaped cells, pleomorphic, with acantholysis features or with giant cells. Usually cancers with superficial infiltration are well-differentiated and cancers with deep penetration are poorly differentiated. In addition, according to the WHO classification the following subtypes of penile squamous cell carcinoma may be differentiated [1]: 1. *basaloid carcinoma*, 2. *warty, condylomatous carcinoma*, 3. *verrucous carcinoma*, 4. *papillary carcinoma*, 5. *spindle cell carcinoma*, 6. *mixed carcinoma*, 7. *adenosquamous carcinoma*.

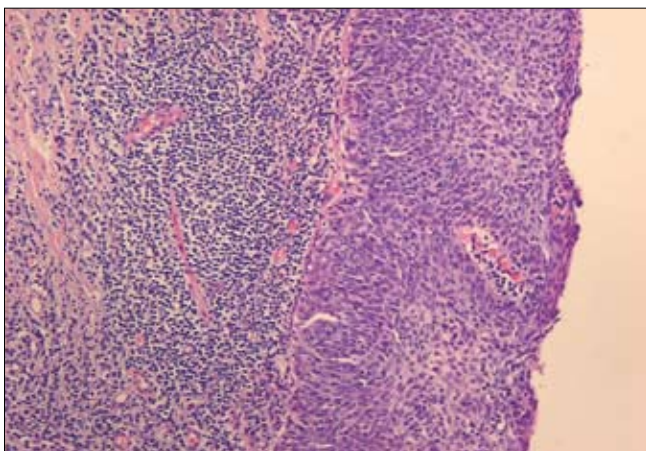


Fig. 2. Penile intraepithelial neoplasia III and HPV (H&E), x 20.

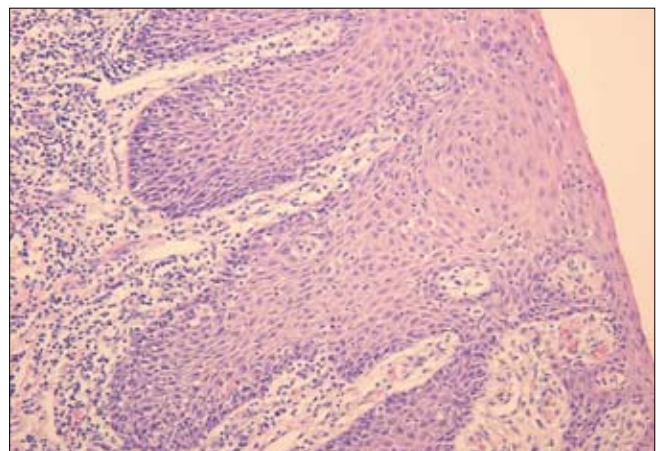


Fig. 3. Penile intraepithelial neoplasia III (carcinoma *in situ*) and negative HPV (H&E), x 20.

Among squamous cell carcinoma variants mentioned before only basaloid and warty, condylomatous carcinomas are associated with an HPV infection. Basaloid carcinoma is an aggressive form corresponding to 5% to 10% of penile cancer cases. The mean age of patients is 60-70 years. The majority of cases develop in the glans area. From a macroscopical point of view, basaloid cancer forms flat and irregular ulcers. Microscopically, its tissue demonstrates solid areas built of small oval and round cells with peripheral palisades. Cancer infiltrations penetrate the surrounding tissues deeply. Inguinal lymphatic node metastases appear. The other type, warty, condylomatous carcinoma, is present in 20% of wart-like forms of penile cancer. Macroscopically, it forms an elevated structure with the diameter of 5 cm. Microscopically, branched, wart-like structures are visible, built from round cells mainly, of low and moderate grade atypia with fibrovascular stroma. There are cancerous cells with koilocytosis. Cancer infiltrations penetrate tissues deeply, there are lymphatic node metastases. Other variants of penile squamous cell carcinoma are not associated with an HPV infection.

HPV infection as a risk factor for penile squamous cell carcinoma. Worldwide literature data published in 2007 indicate a correlation between TP53 protein accumulation, HPV DNA of high risk and Ki-67 proliferative activity in penile cancer. Protzel et al. [2] reported that in 72.7% cases of this cancer HPV DNA mutations, including HPV 16, were detected in 62.5% and HPV 18 in 25% cases. In subsequent reports [3, 4, 5, 6] it was stated that koilocytosis features in cells and an HPV infection are not factors as-

sociated with poor prognosis. The most important prognostic parameter for penile cancer is inguinal lymph node metastases [7]. The 5-year survival in patients without cancer metastases is from 75% to 93%.

CONCLUSION

Chronic infections of the penile mucosa with human papillomavirus increase the risk of neoplastic transformation in the stratified squamous epithelial cells. Other factors also play a role in the development of this cancer. Therefore, microscopic detection of HPV infection determinants such as koilocytosis, dyskeratosis and acantholysis in the cells of stratified squamous epithelium in the penile mucosa, especially in men below 40, may only indicate intraepithelial neoplasia (PIN I – III) which may regress following treatment.

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