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Squamous cell carcinoma of Bartholin gland coexistent with human papillomavirus

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Summary

Squamous cell carcinoma of the Bartholin's glands is a very rare form of vulvar neoplasm. This case presents a 46-year-old female diagnosed with advanced primary squamous cell cancer of the Bartholin glands that has proven positive for human papillomavirus (HPV). The patient was treated with a wide excision of the tumor, an ipsilateral lymphadenectomy, and an adjuvant chemotherapy and irradiation. After two years of follow-up the patient remains in remission.

Key words: Squamous cell cancer; Bartholin's gland; Human papillomavirus.

Introduction

Primary carcinomas of the Bartholin's gland account for 5% of all vulvar cancers and 0.25% of all gynecological malignancies [1]. Squamous cell carcinoma account for approximately 40% of Bartholin gland carcinomas. High risk human papillomavirus (HPV) is investigated as possible cause. Although HPV infection itself does not indicate viral involvement in carcinogenesis, it still points out the possible role of HPV infection as an early step in carcinogenesis, similar to the vulvar one, marking HPV 16 and 18 as most significant ones [2,3]. Carcinoma of the Bartholin gland usually manifests as an enlargement it the gland area and may appear to be a Bartholin cyst. The average age of women with this tumor is 50 years, with most between 40 and 70 years. Bartholin gland tumors area typically solid, deeply infiltrative, and occupy the site of the gland, occasionally obscuring its presence. They range from one to seven cm in diameter [4]. Their clinical presentations include arising tumour mass, pain, pruritus, bleeding, discharge, or their combination. In as many of 50% of patients, there is an initial misdiagnosis of Bartholin's gland cyst or abscess, resulting in diagnostic and therapeutic delay [5].

Case Report

In this report the authors present a case of 46-year-old female, with two childbirths in her medical history. Patient underwent conization because of a CIN III 20 years prior, and hysterectomy without adnexectomy two years prior due to uterine myoma. Patient is also being treated for insulin-dependent diabetes mellitus.

Patient was admitted to the present Department complaining of a painless mass in the Bartholin gland area. Further inspection showed that the greater labia were mildly bulging, the skin color was regular, and that there was no sign of Bartholin gland abscess. By palpation the authors had ruled out the presence of a cyst in the gland's secretory duct; however, a solid, painless six cm mass was discovered. This tumour mass was attached to deeper structures and immobile. Palpation of the inguinal areas had also revealed enlarged and fixated lymph nodes, with no exulceration on the surfaces. After clinical examination, the existence of a tumor in the pelvis and distant metastasis was ruled out, and radical excision and ipsilateral lymphadenectomy were carried out. The tumor was solid, six cm wide, and showed invasive growth into the surrounding adipose tissue in a deep and irregular infiltration manner. The suspicion of a primary malignant tumor of the Bartholin gland was confirmed by a histopathological diagnosis. It was a moderately differentiated squamous cell carcinoma (Figure 1). Qualitative immunohistochemistry analyses of the histological preparations were carried out on p16 (CINtec), which was diffusely positive in all layers of the epithelium (Figure 2), and on the proliferation marker Ki67, which also showed increased expression (Figure 3). Of the twelve inguinofemoral lymph nodes removed, eight were infiltrated by the tumor, and two had their capsules destroyed. After surgical treatment, adjuvant chemoirradiation was applied (cisplatin + RT 45 Gy). Irradiation was applied to the areas of the tumor site, the vulva, the inguinofemoral region, and the pelvis. Two years after treatment, the patient is showing no signs of disease.

Discussion

The differential diagnosis for a Bartholin gland tumor most commonly includes cysts and abscesses, which occur in 2% of women, and other vulvovaginal disorders, such as vulvar carcinoma, acrochordons, hidradenomas, other dermatoses, and condyloma acuminata. The Bartholin gland is composed of columnar epithelium and the ducts are lined by stratified

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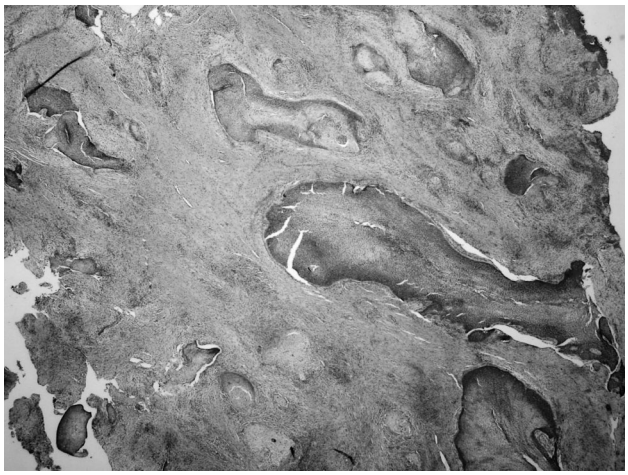

Figure 1. — Squamous cell carcinoma of the Bartholin gland, HE x20.

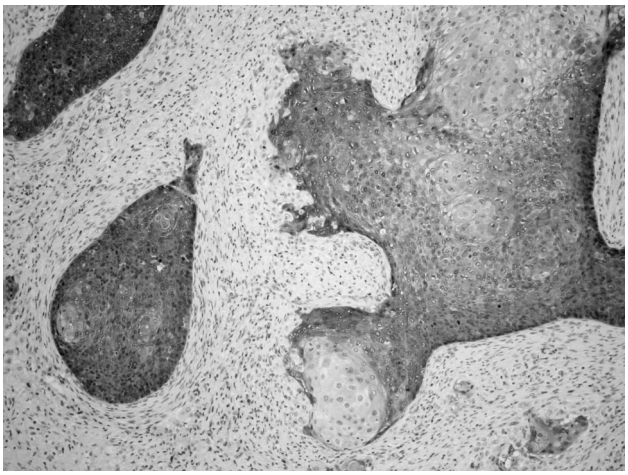

Figure 2. — Squamous cell carcinoma of the Bartholin gland - immunohistochemistry, CIN-tec p16, x100 - diffusely positive in all layers of the epithelium.

squamous epithelium, which changes to transitional cell epithelium toward the terminal ducts. According to Pinn *et al.,* squamous cell carcinoma is the only lesion of the Bartholin gland linked to HPV [6]. The criteria that have to be met for the diagnosis of a primary carcinoma of the Bartholin gland, according to Chamlian's and Taylor [7], are:

1. Transition between normal gland and tumor
2. The tumor involves the area of Bartholin's gland, is histologically compatible with Bartholin origin, and there is no evidence of a primary tumor elsewhere [5].

The criteria for the diagnosis of a primary carcinoma of the Bartholin gland have been met in this case.

Squamous cell carcinoma account for approximately 40% of Bartholin gland carcinomas, the same as adenocarcinomas. Other types include adenoid cystic carcinoma (15%), transitional cell carcinoma (less than 5%), adenosquamous carcinoma (less than 5%), and poorly differentiated adenocarcinomas [4].

The questions arising from this are: Why is there a squamous cell carcinoma in the gland? What is the pathophysiology of this process? What is the origin of a tumor of this cytological type?

Bartholin's gland carcinomas can be squamous if they originate near the orifice of the duct, papillary if they arise from the transitional epithelium of the duct, or adenocarcinomas if they arise from the gland itself [8].

The research by Felix *et al.* has shown that squamous cell carcinomas and adenocarcinomas of the Bartholin's gland are antigenically similar to one another, but are distinct from the normal squamous epithelium of the vulva and the ducts and acinus of Bartholin's gland, and are similar to the epithelium of the transition zone, which is similar to the transition zone of the uterine cervix [9].

The association between squamous cell carcinomas of the genital tract and HPV has been well established [10].

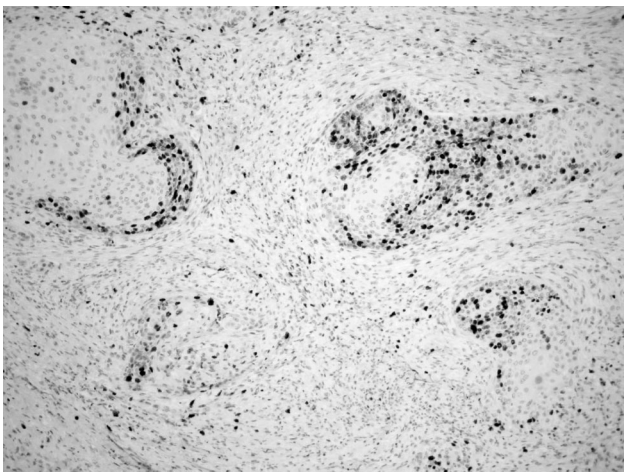

Figure 3. — Squamous cell carcinoma of the Bartholin gland - immunohistochemistry, Ki67, x100.

Research done by Felix *et al.* has shown that six of seven squamous carcinomas of Bartholin's gland contained the HPV DNA. Both the squamous cell and adenocarcinoma seem to be arising from the same cell type, and it could be said that, as in the cervix, both originate in the transitional zone, and are associated with HPV infections [9].

In order to determine the connection between the squamous cell carcinoma and the transforming HPV infection, CINtec p16 immunohistochemistry was used as a way to indirectly determine oncogenic activity of high-risk HPVs. Overexpression of the p16 biomarker is the direct consequence of loss of control of the cell cycle, caused by HPV oncoproteins. As a result of the loss of cell cycle control, accelerated proliferation occurs, which manifests as overexpression of Ki-67 [11].

Immunohistochemistry with p16 has shown, in the present preparation (Figure 2), overexpression and diffuse positivity in all layers of the epithelium, along with a heightened Ki-67 expression (Figure 3), all of which are simultaneous signs of a transforming infection, progression, and proliferation. It is interesting to note that the patient was treated much earlier with conization due to CIN 3 of the cervix. This is often found in other authors' reports on primary carcinoma of the Bartholin gland as a sign of a general infection of the genital tract with HPV, and speaks in favor of the statement that HPV is the cause of the primary squamous cell carcinoma of the Bartholin gland. These results also open a new topic: is there a real possibility for prevention of primary squamous cell carcinoma of the Bartholin gland (along with cervical cancer) by using HPV vaccination?

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