CASE REPORT

Squamous Cell Carcinoma arising on a Background of Vulval Crohn's Disease: A Case Report and Review of the Literature

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ABSTRACT

We present the rare occurrence of squamous carcinoma of the vulva arising on a background of Crohn's disease. Discussion regarding pathogenetic mechanisms is given with a review of the current medical literature.

Key words: Crohn's disease, squamous cell carcinoma, VIN, vulva

INTRODUCTION

Vulval cancer is rare, with an estimated incidence of 3.7/100,000 in the UK, affecting predominantly elderly women.[1] However, there appears to be a rising incidence in the 40–49 years age bracket which likely reflects rising rates of infection with human papillomavirus (HPV).[1] There is little reported in the literature regarding an association between Crohn's disease (CD) and vulval squamous cell carcinoma (SCC). We report a case of vulval SCC in a 47-year- old female arising in a background of vulval CD.

CASE REPORT

A 47-year-old woman with a 32-year history of CD was admitted under the care of the surgical gynecological oncologists for excision of an exophytic tumor of the right labia. She had been symptomatic with vulval irritation over the prior 4 years and had had regular follow-up with the gynecologists. A warty lesion arising on a background of erythematous, ulcerated right labial mucosa was detected during clinical follow-up. The warty lesion was biopsied and diagnosed as moderately differentiated keratinizing squamous carcinoma by the histopathologist.

Our patient had a medical history of surgical treatment for complications of CD affecting the small bowel and rectum, including excision of a complex rectovaginal fistula. She had been on azathioprine monotherapy for 16 years. There was also a history of prior HPV-related cervical disease with three cervical cytology specimens showing low grade, koilocytic dyskaryosis. She received cold coagulation therapy in colposcopy for cervical intraepithelial neoplasia. She had no family history of malignancy.

SURGICAL HISTOLOGY

The radical vulvectomy specimen contained an 8 cm exophytic, solid, and white papillary tumor involving the right labia minora and majora extending to the right perineum and the right side of anal margin.

Histological examination of the resection specimen confirmed a moderately differentiated keratinizing SCC [Figure 1]. No lymphovascular space invasion was seen. The tumor and background high-grade and usual-type vulval intraepithelial neoplasia (VIN3) [Figure 2] were completely excised. Widespread non-necrotizing granulomatous chronic inflammation was present in all sections of the vulva and perineum, extending into vaginal and urethral soft tissue, anus, and rectum. Groin lymphadenectomy was negative for lymph node metastases.

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Immunohistochemistry performed on the invasive SCC showed strong, diffuse positive staining for p16 [Figure 3]. p53 immunohistochemistry showed wild-type expression with occasional nuclear positivity of variable intensity [Figure 4]. A similar pattern of staining was demonstrated in the background VIN with strong and diffuse block staining for p16. The immunohistochemical staining profile confirmed usual-type VIN and suggested an HPV-driven pathogenesis in this case.

DISCUSSION

Over 90% of vulval cancers are of squamous differentiation. Most arise from VIN. There are two distinct pathways to the development of VIN and therefore vulval SCC: HPV related and non-HPV related.[2,3]

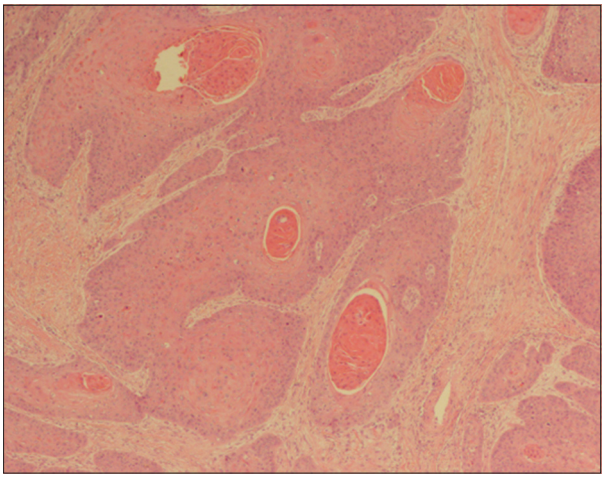

Figure 1: Right labial sections: Histological confirmation of squamous cell carcinoma with areas of keratinization (H and E, ×10)

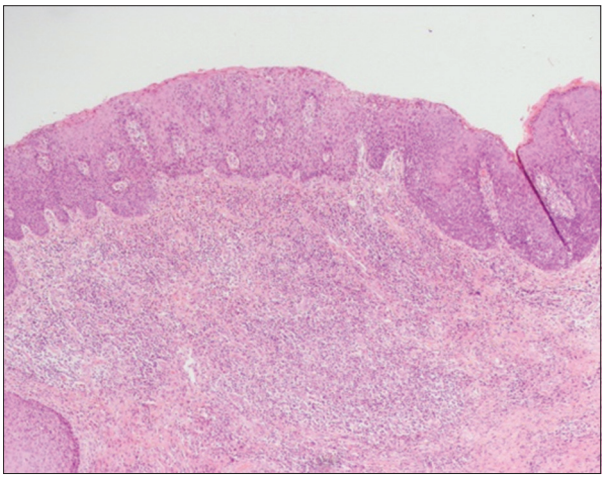

Figure 2: Vulval intraepithelial neoplasia 3 with underlying granulomatous inflammation consistent with active Crohn's disease (H and E, ×10)

The HPV-related pathway tends to occur in younger women. It is most strongly associated with HPV serotypes 16 and 18 and usually produces warty or basaloid SCC. HPV-related SCC arises from usual-type VIN.[2] Histological assessment of high-grade VIN (VIN 2-3) shows hyperchromatic nuclei with a high nuclear-to-cytoplasmic ratio, increased mitotic activity, including abnormal forms, and diffusely positive immunohistochemical staining with p16, as in our case.

In contrast, the non-HPV-related pathway occurs independently of HPV infection, usually in older women on a background of chronic non-neoplastic epithelial disorders, most frequently, lichen sclerosis.[3] VIN in this group is termed differentiated VIN (dVIN) and typically shows subtle features histologically.[4] It is characterized by elongation of rete ridges, abrupt squamous epithelial maturation, dyskeratosis, thick parakeratosis, and excessive spongiosis relative to the surrounding inflammation. dVIN is by definition a high-grade lesion. It is a high-risk lesion

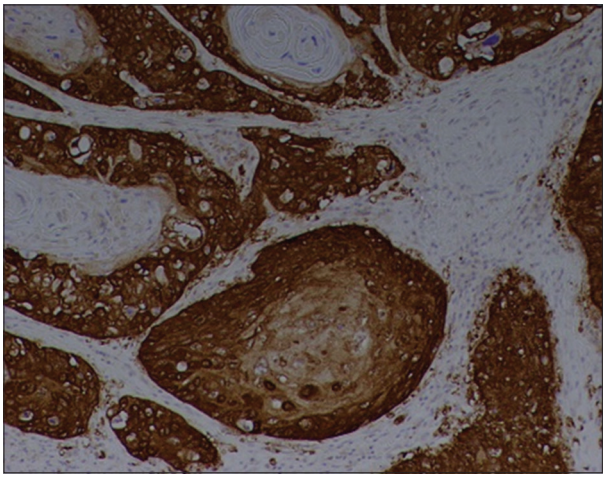

Figure 3: 3p16 immunohistochemical staining of the squamous carcinoma (×10)

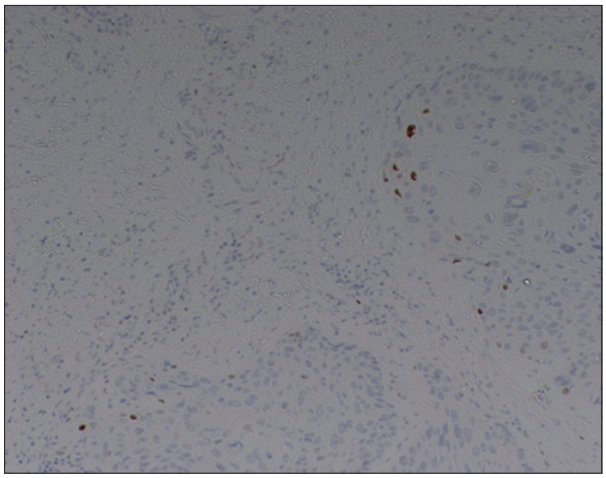

Figure 4: Wild-type p53 of the squamous carcinoma (×10)

for developing into invasive SCC and in a shorter time frame compared with usual-type VIN.[4,5] Squamous carcinomas which develop in this group are usually well differentiated and keratinizing in microscopic appearance.[3] dVIN tends to show mutant p53 and negativity for p16 which aids diagnosis and distinction from usual-type VIN.[4]

The histological findings from our case suggest that the vulval SCC has developed through the HPV-related pathway given the strong diffuse positive staining for p16 and wild-type p53 for both the SCC and background VIN. However, in the context of long-standing CD, it is possible that other factors have compounded the risk of developing SCC.

SCC arising in areas of chronic inflammation is not uncommon.[6] The hypothesis that chronic inflammation is associated with the development of malignancy has been around since Virchow in 1863.[7] The mechanism by which this occurs is complex but is thought to result from local repeated tissue damage and regeneration in the presence of reactive nitrogen and oxygen species released by inflammatory cells causing DNA alterations[6] alongside the modulation of oncogenic signaling pathways, whereby the activation of transcription factors and accumulation of tumorigenic factors cause suppression of antitumor immune responses resulting in tumor development.[8]

It has been reported that a variety of chronic inflammatory processes in the perineal region have a propensity for malignant degeneration to SCC,[9,10] and indeed, a case of vulval SCC arising in an area of chronic hidradenitis suppurativa in a patient with a long history of CD has been reported.[11] Case reports of vulval adenocarcinoma arising in a background of CD exist,[12] but there is little documented in the literature regarding a direct association between CD and vulval SCC. However, the link between CD and anal SCC is well demonstrated.[13,14] The annual incidence of anal SCC in CD is around twice the rate of that of the general population.[13,15] The majority of cases occur in association with long-standing (>10 years) CD, underlying chronic perianal disease 15 and HPV infection in between 40% and 50% of cases,[13,16] but sample sizes have been small.

Immunosuppression, as a result of a chronic condition or due to immunosuppressant medication, facilitates oncogenesis through suppression of antitumor mechanisms.[17] A meta-analysis by Allegretti *et al*. showed that prolonged immunosuppressant therapy in inflammatory bowel disease could increase the rate of HPV-associated cervical dysplasia and cancer (odds ratio 1.34)[18] Moreover, a study by Huftness *et al*. has demonstrated an odds ratio for inducing cervical cancer of 1.65 for 5-aminosalicylic acid and 3.45 for azathioprine.[19] However, further, investigation is required as these findings have not been found consistently and therefore should be interpreted with caution. In our case, the use of azathioprine may have contributed to the development of usual-type VIN through immunosuppression and an increased susceptibility to acquiring HPV. This has been documented in HPV-related penile squamous carcinoma in a patient with ulcerative colitis.[20] It is not possible to quantify the direct effect of long-standing CD on the pathogenetic mechanisms, leading to invasive squamous carcinoma.

CONCLUSION

Based on the histological findings, the HPV-related pathway is likely to represent the etiological process for the development of vulval SCC in this case. Although little has previously been reported in the literature regarding an association between CD and vulval SCC, it is reasonable to postulate that the chronic inflammatory nature of CD alongside prolonged immunosuppressant therapy creates a haven for infection with HPV, enabling transformation to VIN and then invasive SCC. The risk of malignant transformation of vulval lesions in patients with vulval CD should therefore be appreciated when planning clinical follow-up of such patients.

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