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Case Report

Negative p53 expression and negative high risk HPV in a 26-year-old lady with vulvar keratinizing squamous cell carcinoma: report of a case

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Summary

Vulvar intraepithelial neoplasia (VIN) and human papilloma virus (HPV) are the main pathways for development of vulvar carcinoma in young women. While, non-HPV associated pathway is the usual pattern seen in postmenopausal women. Herein, the authors report a case of 26-year-old lady with keratinizing vulvar squamous cell carcinoma (SCC), in which vulvar intraepithelial neoplasia (VIN) of the simplex type and p53 expression were absent. Moreover, no high risk HPV was detected by the highly sensitive real time-polymerase chain reaction (RT-PCR) technology on the paraffin embedded tumor tissue. Therefore, in addition to the patient's young age, she had morphologic and molecular patterns that are usually seen in elderly women. The authors believe that this is an unusual presentation in such a very young lady. The cause of this cancer in this case is not completely understood and indicates the necessity to sample any suspicious lesions at this site at any age.

Key words: Juvenile vulvar carcinoma; Human papilloma virus; Juvenile keratinizing squamous cell carcinoma; Polymerase chain reaction; Immunohistochemistry.

Introduction

Carcinoma of the vulva is the fourth most common gynecologic malignancy in the United States according to the most recent cancer statistics [1]. It is an unusual tumor with an incidence of 1.5 per 100,000 women per year in the USA [2]. Squamous cell carcinoma (SCC) constitutes about 80% of cases of vulvar cancer, of which 20% are associated with human papilloma virus (HPV) and primarily affects younger women [3]. However, most cases of vulvar carcinoma are seen in postmenopausal women and are not HPV related [3]. SCC is only rarely seen in patients under the age of 30 [4].

There are two distinct pathways for vulvar SCC. The first one and less common affects young women from 35-65 years of age and involves HPV, mostly of the serotypes 16 and 18 [5]. This subtype usually has warty or basaloid histology [2] and is associated with adjacent warty or basaloid vulvar intraepithelial neoplasia (VIN). The second type affects women at advanced age (55-85 years), is more common, typically shows a low rate of HPV infection [5] and higher rates of p53 mutation, adjacent VIN of the simplex type and tends to be of keratinizing morphology [2]

There is ongoing evidence that vulvar SCC and its precursor lesion (VIN) are increasing, particularly in young women [1, 6]; the reasons for this increase may be attributed to HPV infection and the change in behavior facilitating its transmission [6].

Herein we report a case of vulvar invasive SCC of the keratinizing type, occurring in a 26-year-old young lady with no known chronic illnesses, in which the histological and associated viral features are those seen in the elderly age group.

Case Report

A 26-year-old lady, nullipara, married for six months, non-smoker, previously healthy, presented to the gynecology clinic of the present university hospital, complaining of a non-healing ulcer of the vulva. On physical examination, an ulcer was seen located at the labia majora. No clinically evident changes of skin dystrophies were noted. The inguinal lymph nodes were non palpable. An excision biopsy was taken from the ulcer and sent for pathology assessment. Later, the patient was tested for human immunodeficiency virus (HIV) status and was negative. Radiologic studies failed to show any evidence of a distant metastasis or even a remote primary skin carcinoma. Gross examination of the formalin fixed excision biopsy specimen revealed a fragment of skin with overlying ulcer. The overall specimen measured 2.2×1.3×1 cm.

A diagnosis of ulcerating moderately differentiated keratinizing SCC was made upon histological examination (Figures 1 and 2). The horizontal diameter was 11 mm, and depth of invasion was 8 mm (measured from the epithelial–dermal junction of the adjacent-most superficial dermal papillae to the deepest point of invasion). Lymphatic invasion was present (Figure 3). The adja-

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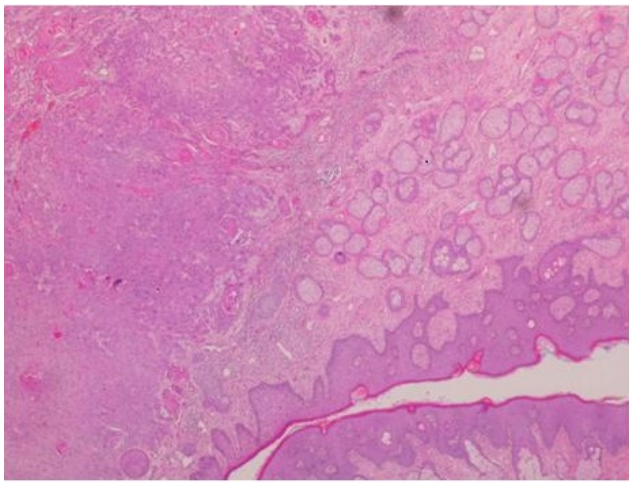

Figure 1. — Invasive moderately differentiated SCC. H&E stain (magnification ×10).

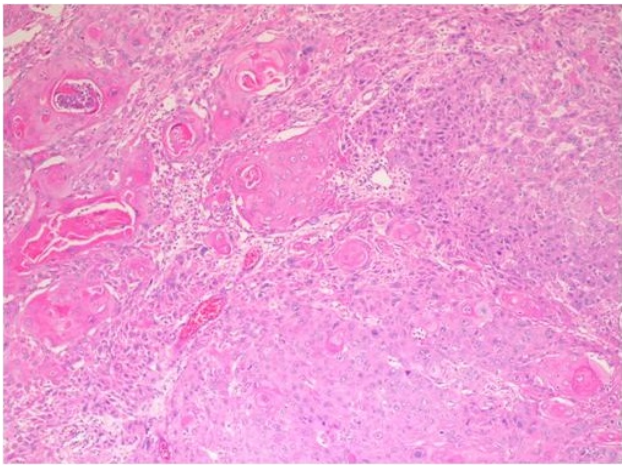

Figure 2. — Invasive keratinizing moderately differentiated SCC. H&E stain (magnification ×40).

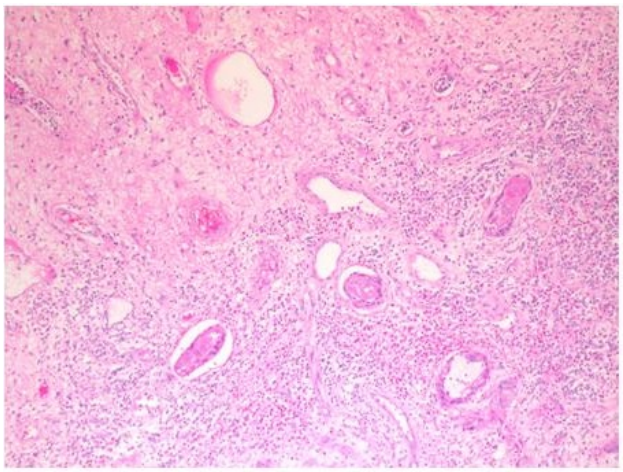

Figure 3. — Lymphovascular invasion. H&E stain (magnification ×40).

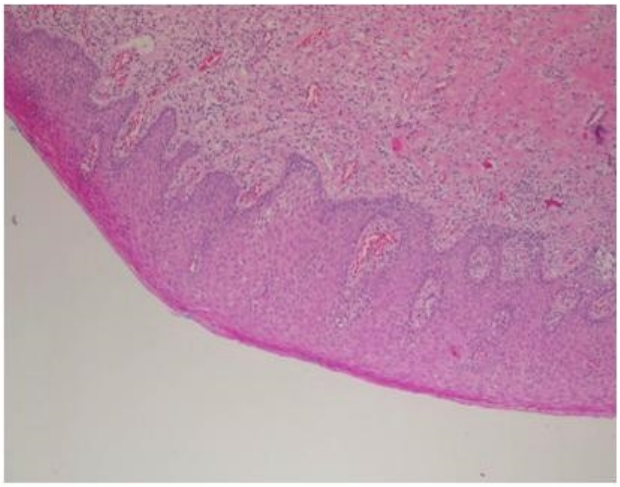

Figure 4. — Adjacent squamous hyperplasia without atypia or koilocytic changes. H&E stain (magnification ×10).

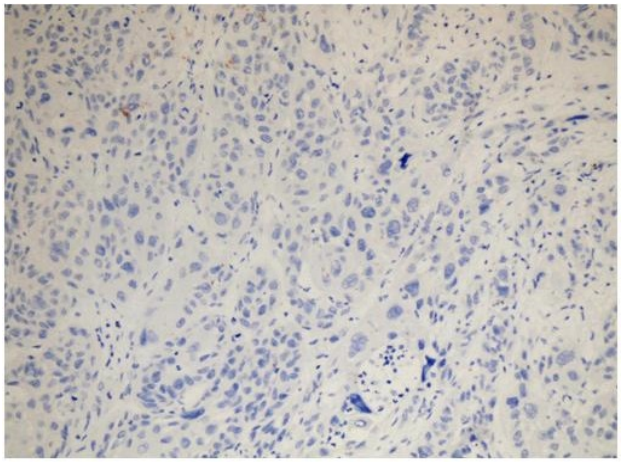

Figure 5. — Negative immunohistochemical reaction for p53 immunostains (×40).

cent vulvar epithelium showed mild squamous hyperplastic changes (vulvar keratosis), without koilocytic changes (Figure 4). Vulvar intraepithelial neoplasia (VIN) of the warty, basaloid or simplex subtypes were not identified. All resection margins were free of invasive carcinoma and the lesion was completely excised. No lymph nodes were submitted for evaluation.

Negative immunohistochemical expression for p53 in the invasive tumor and the adjacent epithelium is seen (Figure 5). In addition, no immunostaining for HPV-16 was detected.

Extraction of DNA was performed from formalin fixed paraffin embedded (FFPE) tumor tissue. Tissue kit from QIAGEN was used. Real time-polymerase chain reaction (RT-PCR) for detection of high risk HPV genotypes was carried out on the extracted DNA using Rotor- Gene (RT- PCR) instrument based on Taqman probe chemistry. The quality of the extracted samples was assayed versus an internal control in the same sample to assure the quality and enough quantity in the same run. The tumor tissue was negative for tested HPV DNA high risk genotypes.

Discussion

Although VIN and SCC are increasing in incidence in young women in recent years [1, 2, 4], the diagnosis of vulvar SCC in young women under the age of 35 is still rare[4].

These cases are usually associated with high risk HPV infection and are of the basaloid or warty histomorphology. [2] Keratinizing SCC in this age group is rarely seen. The keratinizing subtype is the pattern diagnosed in the post-menopausal age group, and is usually associated with VIN of the simplex type, adjacent changes of vulvar dystrophies such as lichen sclerosus and squamous hyperplasia (vulvar keratosis), and is usually not associated with HPV infection [7]. This subtype is frequently associated with p53 mutation and expression [2, 4] Nonetheless, none of these factors were present in this case, aside from the mild adjacent squamous hyperplasia, to appropriately explain the mechanism of the disease in this young lady.

The patient is peculiar not only in the very young age of presentation, but also in the keratinizing morphology and the HPV negative status that are classically seen in elderly patients. Moreover, the absence of p53 expression also indicates a non-understood pathway of tumor genesis.

In an attempt to find a risk factor related to the present patient's condition, a thorough review of the clinical and radiologic history along with laboratory workup failed to reveal any previous history of immunodeficiency, particularly HIV testing was negative. This case showed prominent lymphovascular invasion. However, evidence of a distant metastasis or even a remote primary skin carcinoma was not present.

Although many cases of vulvar squamous cell carcinoma in young women, notably aged less than 35 years, have been reported in literature, only few are of the HPV negative subtype or the keratinizing morphology. Additionally, most of the reported cases show a positive history of depressed immune status or HIV infection.

In a clinicopathologic study of 21 cases of vulvar SCC in patients younger than 40 year of age, performed in British Columbia Cancer Agency (BCCA) during the period 1970–1998, only three cases were associated with simplex VIN, and three out of 20 cases tested for HPV DNA were negative [8].

A thorough search in PubMed was undertaken, and only a few cases of vulvar SCC in young women negative for HPV and showing neither warty nor basaloid histopathologic patterns were found. One case was very similar to our case and was diagnosed in a 26-year-old lady with HPV negative status and keratinizing morphology [4]. However, focal VIN of the simplex type and diffuse immunostaining for p53 were associated. Another keratinizing SCC with adjacent simplex VIN was reported in a 28-year-old lady with immunostaining profile suggestive of a non-HPV dependent pathway. Moreover, this case was also negative for HPV by PCR [7]. Additionally, a report of a 35-year-old virgin patient with Turner syndrome and vulvar well-differentiated SCC was also unusual and lacking any of the risk factors known for this type of malignancy [9].

A recently published two reports of a 34-year-old lady with an HPV-negative well-differentiated SCC [10] and a 44-year-old with keratinizing vulvar SCC not associated with anogenital HPV related disease [11] add to the series, respectively. The second case surprisingly presented as neglected dermatitis [11]. Moreover, another two cases were reported in 1991 [12] of a 22-year-old lady, with a well-differentiated keratinizing SCC and lichen sclerosus as an associated disease, and a 16-year-old lady with well differentiated SCC and negative HPV status by in situ hybridization. Few other reported cases of vulvar SCC in young patients were found. However, a substantial number of them were reported in association with HIV infection [13-17]. Some reported cases were also strangely diagnosed during pregnancy [18-20]. Moreover, other reported cases were diagnosed in the setting of an associated immune mediated disease like Crohn's disease [21], systemic lupus erythematosus (SLE) [22], Recurrent Bone Marrow Hypoplasia [23] or Fanconi anemia [24].

The case presented here cannot be totally explained by any of the theories reported so far, especially the absence of p53 immunohistochemical expression in this morphologically keratinizing subtype. Other risk factors such as cigarette smoking, multiple sexual partners, and genital warts were also absent in this case. So that new theories may be needed to investigate such pattern of presentation in a very young lady with HPV negative tumor, especially in view of similar reported cases in literature.

In conclusion, biopsy from any suspicious lesion in the vulva is mandatory, even in young ladies regardless of the relative rarity of this type of tumor in this age, in order to avoid delay in diagnosis and management. Also, it is important to assess the HPV status in such patients. Since HPV- related tumors require follow up and monitoring over a long period of time to check for recurrence or development of other synchronous or metachronous HPV associated tumors of the vulva and other sites in the lower anogenital tract.

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