A Precursor to HPV-Independent VSCC : Differentiated Exophytic Vulvar Intraepithelial Lesion - A Case Report

Weiping Zheng

Shaoxing People's Hospital

Minhua Li (✉ jiangling817@hotmail.com)

Shaoxing University Affiliated First Hospital: Shaoxing People's Hospital

Case Report

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Abstract

Background: Vulvar cancer is a relatively rare gynecologic malignant disease. The majority of these tumors are vulvar squamous cell carcinoma (VSCC). There are two distinct aetiopathogenic pathways leading to VSCC: human papillomavirus (HPV)-dependent and HPV-independent. The precursor lesions of HPV-independent VSCC include differentiated vulvar intraepithelial neoplasia(VIN), vulvar acanthosis with altered differentiation(VAAD) and differentiated exophytic vulvar intraepithelial lesion(DE-VIL) . To date, the report of DE-VIL has not been found after this term was proposed in 2017. So it usually has been under-recognised by pathologists in the past owing to the incidence of DE-VIL is relatively small.

Case presentation: Here, we report a typical case of DE-VIL, which exhibits the absence of HPV infection and mutations in TP53. Interesting, a small lesion showed similar morphologic feature to HSIL nearby the lesion of DE-VIL. However, it showed same immunochemical patterns with DE-VIL. To date, no other study has reported this phenomenon. Whether it is a rare subtype of DE-VIL or only a accompanying status is still unclear.

Conclusions: As the precursor lesions of HPV-independent VSCC, DE-VIL was too difficult to diagnosis due to the lack of sufficient evidence. Therefore, we should pay more and more attention for DE-VIL.

Introduction

Squamous cell carcinoma(VSCC) account for 83% of all malignancies in the vulva[1]. In 1981, vulvar intraepithelial neoplasia(VIN) was introduced into medical terminology, which derives from cervical intraepithelial neoplasia(CIN). Currently, VIN is regarded as the popular term for squamous cell premalignant disease of the vulva.

There are 2 types of VIN and they have been well recognized. The usual type is known as warty-basaloid or undifferentiated VIN, which is associated with HPV. The other type is termed differentiated or simplex VIN, which is not associated with HPV[2]. Recently, a new precursor have elucidated by some explorations. Differentiated exophytic vulvar intraepithelial lesion(DE-VIL) was initially derived from a group of “atypical verruciform lesions” and define this group as manifesting with (1) verruciform morphology, (2) abnormalities in keratinocyte and differentiation, (3) absence of conspicuous basal atypia, (4) a high frequency of PIK3CA mutations, (5) absence of TP53 mutations[3]. It failed to meet criteria for VIN (differentiated or usual type). Moreover, it displayed histologic overlap with vulvar acanthosis with altered differentiation(VAAD) and Verrucous carcinoma(VC)[4].

As the putative precursor lesion to a subset of well differentiated VSCC, DE-VIL exhibits neither HPV infection nor mutations in TP53[5]. To date, the report of DE-VIL has not been found after this term was proposed in 2017. The recognition of DE-VIL is a challenge, even for experienced gynaecological pathologists owing to it is very difficult to distinguish from other similar lesions. However, the patient with HPV-independent VSCC have a worse prognosis compared with HPV-associated VSCC[6]. Therefore, more

and more attention should been paid for DE-VIL, which acts as one of precursor lesions to HPV-independent VSCC.

Case Presentation

Clinical history

A 63-year-old female was admitted to our hospital with a chief complaint of vulvar pruritus for two years duration. All of the other tests were within the normal limits. The pathological biopsy of vulvar hinted the possibility of HSIL/VIN III. So surgical resection of the lesion was performed. Gross examination revealed multi-focal grey-white or erythematous macules or verrucous plaques, which were mainly lying on either side of labia majora.

Pathological findings

For the case, the hematoxylin and eosin slides were reviewed for confirmation of the diagnosis by three pathologists. Microscopy revealed a distinct non-invasive squamous epithelial proliferation with verruciform architecture(Fig. 1A). Prickle cell layer was thicken and showed clavate growing pattern(Fig. 1B). Part of the lesions showed multilayered parakeratosis and loss of the granular cell layer with superficial epithelial pallor(Fig. 1C). Some scattered cells showed dyskeratosis in the lesion(Fig. 1D). Only minimal basal atypia was showed in some areas. Conspicuous basal atypia and human papillomavirus-associated histomorphologic changes were absent in the lesions(Fig. 1E). Moreover, lichen sclerosus(LS) was not been found in the background of the lesions. However, small obvious cytological atypia extending into the upper layers of the epithelium was found in the vicinity of verruciform lesion, mimicking HSIL(Fig. 1F). Moreover, immunochemical patterns in this small lesion was concordant with the main lesion.

In our case, the major immunochemical patterns was seen as follows: 1)partly weak staining of P53 was revealed (TP53 mutations must be strong or completely no staining), hinting the absence of TP53 mutations or wild type of P53(Fig. 2A,D). 2)weak staining of p16 was showed(the positive staining pattern must be strong, diffuse and continuous), so defining the negative expression of p16(Fig. 2B,E). 3)Ki-67 stains the nearly full thickness of the epithelium(Fig. 2C,F).

It failed to meet criteria for VIN (differentiated or usual type).It showed the similar features with DE-VIL.Therefore, we made a diagnosis of DEVIL in this patient.

Follow-up data have shown no signs of local recurrence or metastasis at up to 10 months after complete surgical removal.

Discussion

Currently, the pathogenesis of vulvar cancer is dichotomous. Usual-type VIN(uVIN) are usually defined by high-risk HPV infection. Differentiated vulvar intraepithelial neoplasia(dVIN)are associated with TP53

mutations. However, there are a significant, albeit small, subset of vulvar carcinomas exhibits the absence of HPV infection and mutations in TP53. In such occasions, the term 'atypical verruciform hyperplasia' is often applied. In 2017, CP Crum et al propose using the term 'DE-VIL' to redefine these atypical verruciform lesion group owing to their unique morphologic and genetic characteristics relative to differentiated and usual VIN [3].

DVIN, VAAD and DE-VIL were belong to the precursor lesions of HPV-independent VSCC[7]. DE-VIL show prominent acanthosis and papillomatosis, but minimal atypia. Complete loss of the granular layer in some areas often been showed in DE-VIL. Due to its presence of plaque-like parakeratosis, lack of atypia, lack of premature keratinisation and the background of lichen sclerosis(LS) as seen in dVIN, it is different from dVIN[8]. Meanwhile, high nuclear-to-cytoplasmic ratios, pleomorphism, hyperchromasia, apoptotic bodies and mitoses are also absent, hinting that DE-VIL is completely different from uVIN. In this study, our case report showed the similar features,meeting the criteria for DE-VIL.However, an interesting detection was that small significant cytological atypia extending into the upper layers of the epithelium was showed in the vicinity of verruciform lesion, mimicking HSIL. And the same immunochemical patterns was showed in this small lesion when compared with the verruciform lesion.Whether it is a rare subtype of DE-VIL or only a accompanying status is still pending. To date, no other study had reported this phenomenon. Someone suggested that the morphological features of HPV-independent and HPV-associated precursor lesions can overlap, based on HE Staining[7]. Perhaps, it can be used to explain that phenomenon in our case report.

As the important differential diagnosis of DE-VIL,VAAD should been paid more attention for gynaecological pathologists. Although a vast majority of VAAD lesions displayed histologic overlap with DE-VIL. Some molecular studies showed that they maybe two unique entities. Specifically, VAAD has been showed a high percentage of HRAS (71.4%) and NOTCH1 (28.6%) mutations[9]. However, DE-VILs are associated with activating PIK3CA mutations, which have been revealed in 73% of lesions, and only 7% of lesions have identified HRAS mutations [4]. Some authors prefer the term DE-VIL over VAAD when the criteria for DE-VIL are met for diagnostic purposes[5]. Due to the rare occurrence of DE-VIL, further studies are required to reveal the difference between these lesions.

A growing number of relevant studies have focused on genetic and epigenetic alterations in vulvar cancer. TP53 mutations and HPV status may play important roles in the carcinogenesis of VSCC[10]. There were many studies reported positive expression of p53 in 66–100% of dVIN[11–13]. Meanwhile, Trietsch et al stated TP53 mutations were showed in 3% of HPV-positive VIN and 21% of HPV-negative VIN [10]. So it was obvious that part of HPV-independent VSCC didn't follow the TP53 pathway. DE-VIL exhibited the absence of HPV infection and mutations in TP53, it was concordant with that result. On the other hand, as a surrogate marker for high-risk HPV infection, the positive expression of P16 associated extremely well with high-risk HPV status [11,12,14]. The positive staining pattern must be strong, diffuse and continuous (nuclear and cytoplasmic). Otherwise, we should assess the negative staining of P16. Our case showed wild-type p53 immunostaining and negative expression of P16,so further support the diagnosis of DE-VIL.

Positive staining of Ki-67 in the basal and suprabasilar layers was showed in uVIN and dVIN [8]. The staining for Ki-67 is much more conspicuous in uVIN and the full thickness of the epithelium was usually been stained[6, 11, 15]. In contrast to the basal expression seen in LS, positive staining of Ki-67 in dVIN were showed in the basal layer and a thin parabasal layer[6]. In our case, Ki-67 stains the nearly full thickness of the epithelium, suggesting that DE-VIL maybe play an important role in the development of vulvar SCC. Moreover, no lymphatic metastasis or recurrence has been showed in our case to date. Therefore, complete excision and monitoring for progression is recommended in all cases of DE-VIL[5].

In a conclusion, as the precursor lesions of HPV-independent VSCC, DE-VIL demonstrated considerable morphologic overlap with VAAD, so additional study was required to delineate if they are independent entity. Meanwhile, DE-VIL was too difficult to diagnosis due to the lack of sufficient evidence. Therefore, we should pay more and more attention for DE-VIL. Moreover, an interesting phenomenon was found in our report: a small lesion showed similar morphologic feature to HSIL nearby the lesion of DE-VIL. However, it showed same immunochemical patterns with DE-VIL. Explanation of this phenomenon is still unclear, so further investigation is needed.

Abbreviations

VSCC: vulvar squamous cell carcinoma; HPV: human papillomavirus; VIN: vulvar intraepithelial neoplasia; VAAD: vulvar acanthosis with altered differentiation; DE-VIL: differentiated exophytic vulvar intraepithelial lesion; CIN: cervical intraepithelial neoplasia; LS: lichen sclerosis; uVIN: Usual-type VIN; dVIN: Differentiated vulvar intraepithelial neoplasia.

Declarations

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Author contributions

Weiping Zheng, performed the surgery and clinical follow up of the patient. Minhua Li, performed the optical microscopy and scanning electron microscopy analysis. All authors wrote and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

Competing interests

Conflict of interest relevant to this article was not reported.

Author details

Departments of ¹Gynecology, Pathology², Shaoxing People's Hospital & Shaoxing Hospital, Zhejiang University Shool of Medicine, Shaoxing, China.

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Figures

Figure 1

(A)Non-invasive squamous epithelial proliferation with verruciform architecture was revealed($\times 100$). (B) Prickle cell layer was thickened and showed clavate growing pattern($\times 200$). (C)Multilayered parakeratosis and loss of the granular cell layer was showed($\times 400$). (D)Some scattered cells showed dyskeratosis in the lesion($\times 400$). (E)Minimal basal atypia was showed in some areas($\times 200$). (F)Small obvious cytological atypia extended into the upper layers of the epithelium,mimicking HSIL($\times 400$).

Figure 2

(A) Wild type of P53 was revealed in verruciform lesion($\times 200$). (B)Negative expression of p16 was showed in verruciform lesion($\times 200$). (C)Ki-67 stains the nearly full thickness of the epithelium in verruciform lesion($\times 200$). (D)Wild type of P53 was revealed in the small lesion, mimicking HSIL($\times 200$). (E)Negative expression of p16 was showed in the small lesion, mimicking HSIL($\times 400$). (F)Ki-67 stains the nearly full thickness of the epithelium in the small lesion, mimicking HSIL($\times 100$).

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