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Case report

HPV-associated vulvar carcinoma with sebaceous differentiation

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1. Introduction

Sebaceous carcinoma (SC) is an uncommon but potentially aggressive cutaneous malignancy. It is most often categorized as periocular versus extraocular sebaceous carcinoma. SC is thought to arise from sebaceous glands, which are most abundant in the skin of the head and neck but occur throughout the hair-bearing regions of the body (Nelson et al., 1995). Periocular and extraocular SC behave differently, have different genetic signatures, and require different management approaches (Owen et al., 2019). SC has an association with Muir-Torre Syndrome (MTS), a variant of Lynch syndrome caused by DNA mismatch repair (MMR) deficiency with microsatellite instability (John and Schwartz, 2016). Although sebaceous glands are common in the vulva, vulvar carcinoma with sebaceous differentiation (vSC) is rare, with only 16 previous cases reported. Vulvar neoplasms are classified as HPV-associated or HPV-independent by the Fifth edition of the World Health Organization Classification of Tumours of the Female Genital Tract (Höhn et al., 2020). Only recently was HPV demonstrated in association with vulvar sebaceous neoplasia (Hamza et al., 2023). Best management practices for vSC are poorly defined due to the limited case data. We present a case of MMR-proficient, HPV-associated vSC treated by radical vulvectomy with clitorectomy and bilateral sentinel lymph node dissection. We also review existing literature and treatment recommendations for vSC.

2. Case Presentation

A 31-year-old woman with past medical history of herpes simplex virus 1 (HSV-1) infection and human papillomavirus (HPV) status post cervical loop electrosurgical excision procedure presented to Vulvar and Vaginal Disease clinic with complaints of vulvar edema, erythema, and pruritus without discharge for the past year (Fig. 1A). Symptom onset coincided with her first pregnancy. A punch biopsy showed superficial fragments of atypical squamous epithelium but was insufficient for definitive diagnosis. The reported differential diagnosis included herpes simplex infection, pemphigus vulgaris and erosive lichen planus.

The patient was treated with a variety of therapies for presumed unremitting lichen planus with complicating HSV-1 flares and fungal infections. Pharmacotherapy included topical steroids, antifungal, and antiviral medications. However, the patient continued to have severe vulvodynia, ulceration, erythema, and pruritus. Repeat biopsy was performed nine months after the initial biopsy, showing an intraepithelial proliferation of basaloid cells with brisk mitotic and apoptotic activity. The dysplastic cells showed block-like reactivity for p16, with wild-type pattern reactivity for p53. Adipophilin immunostaining performed at an outside institution was positive in foci of sebaceous differentiation. Mismatch repair immunostains (MLH1, PMS2, MSH2 and MSH6) showed retained nuclear reactivity in the dysplastic epithelium. The pathologist rendered a consultative diagnosis of sebaceous carcinoma in situ. HPV in situ hybridization testing was not performed on the

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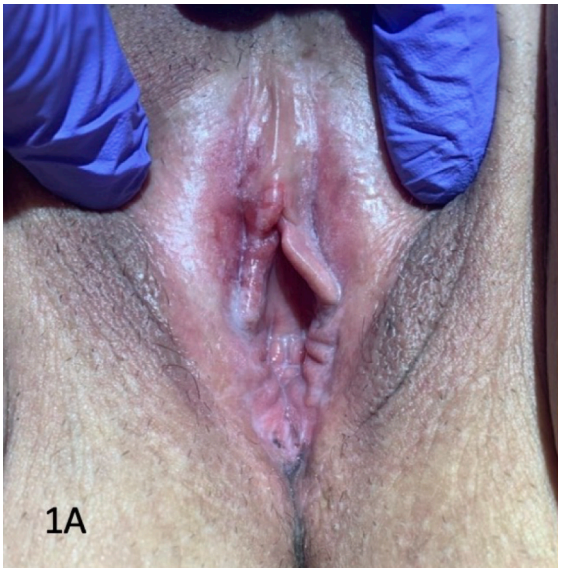

Fig. 1A. Vulvar lesion at initial presentation. Lesion with erythema and pruritus.

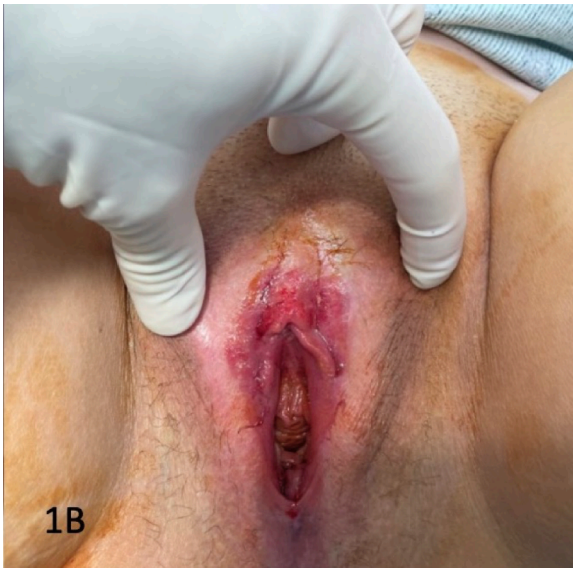

Fig. 1B. Vulvar lesion upon presentation to gynecologic oncology. Taken 11 months after Fig. 1A. Granular, erythematous lesion involving bilateral periclitoral region.

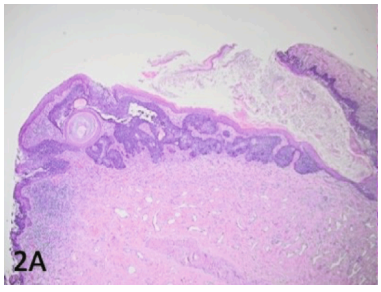

Fig. 2A. Histologic sections of the vulva show basal predominance of dysplastic epithelium, with relative sparing of the superficial squamous epithelium (hematoxylin & eosin, 40x original magnification). The neoplasm somewhat mimics the growth pattern of basal cell carcinoma on low power.

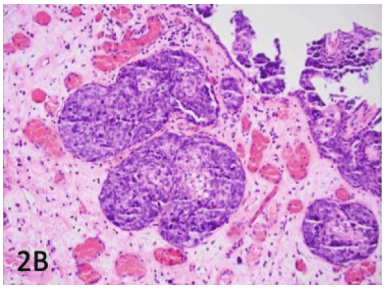

Fig. 2B. Tumor nests contain rare vacuolated sebocytes. The neoplastic cells have brisk mitotic and apoptotic activity (H&E, 200x).

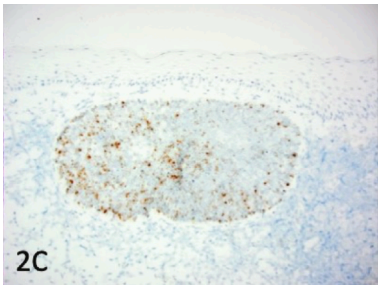

Fig. 2C. In situ hybridization is positive for high-risk HPV RNA cocktail in the neoplastic cells and negative in the overlying surface epithelium (200x).

biopsy material.

The patient was referred to gynecologic oncology (Fig. 1B). She was 20 weeks pregnant at her first oncology visit, complicating management. In consultation with radiology, PET scan for evidence of distant disease was deferred to non-contrast pelvic MRI to minimize risk to the fetus; no metastatic foci were identified on MRI. The patient underwent radical vulvectomy and clitorectomy 9 days later. The vulvectomy specimen was submitted for histologic examination (Figs. 2A and 2B). The specimen was reviewed by multiple pathologists at multiple institutions. Ultimately, expert consultation was an interpretation of invasive squamous cell carcinoma with sebaceous differentiation, with "thickness" of 1–1.5 mm. Multifocal extension into adnexal structures was present. No lymphovascular space invasion was seen. The peripheral margin was involved by intraepithelial carcinoma. The margins were uninvolved by invasive carcinoma. In situ hybridization detected high-risk HPV RNA in the neoplastic cells, supporting classification of the neoplasm as HPV-associated, per the 5th edition of the World Health Organization Classification of Tumours of the Female Genital Tract (Fig. 2C) (Höhn et al., 2020).

Given the depth of invasion (>1.0 mm) and carcinoma measuring less than 4 cm in greatest dimension, decision was made to proceed with bilateral sentinel lymph node dissection (SLND) (Covens et al., 2015). The procedure was delayed until 4 months after initial radical vulvectomy and clitorectomy, as the patient underwent childbirth. SLND yielded five negative nodes (two from the right, three from the left). A PET scan performed one month after SLND showed avidity consistent with postoperative changes in the bilateral groin and activity consistent with postpartum lactational changes in the breasts and axillae, without evidence of metastatic disease. The patient has no evidence of disease at 9 months after radical vulvectomy and clitorectomy.

3. Discussion

In this report, we present a rare case of vulvar carcinoma with sebaceous differentiation in a pregnant patient. Sebaceous differentiation is rare in vulvar carcinomas, with only 17 cases reported, to date (Hamza et al., 2023). Additionally, this patient's case is unique because

Table 1
Vulvar Sebaceous Carcinoma with HPV Association.

References	Year	Age	Lesion	HPV Status	Treatment	Metastasis	Follow-Up	Outcome
Present Case	2023	33	R labia majora and clitoris	Positive high-risk HPV by RNA in-situ hybridization	Radical vulvectomy and clitorectomy with SNB	none to date	seven months	No evidence of disease
Hamza et al. (case 1)	2022	60	Between R labia majora and minora	Positive high-risk HPV by RNA in-situ hybridization	R periclitoral simple partial vulvectomy	None to date	18 months	Recurrent lesion six months postop with Efudex treatment; NED at 1.5 years
Hamza et al. (case 2)	2022	48	R vulva	Positive high-risk HPV by RNA in-situ hybridization	R partial vulvectomy x4 for recurrence	None to date	Five months after last excisional surgery	Recurrence x2, evidence of disease with positive margins

it is the only reported case in which the disease course overlaps with pregnancy and is the third reported case of vSC with HPV association. At her initial presentation, the patient stated that symptoms began when she was seven months pregnant, which was ten months prior to presentation. Then, six months after the initial presentation, the patient became pregnant again.

It is well documented that the female body undergoes significant systemic immunological changes during pregnancy (Abu-Raya et al., 2020). A *meta*-analysis of 28 studies including North America, Asia, and Europe demonstrated that HPV prevalence rates in pregnant women were significantly higher than those in non-pregnant women (Liu et al., 2014). However, there is insufficient causal evidence that a pregnancy state results in increased latent HPV infection or increased HPV plasmid replication. Speculation regarding this association centers mostly around the effect of a high estrogen state, which pregnancy is considered to be. Studies in HPV-16 positive cell lines CaSki and SiHa demonstrated that estrogen increased proliferation of SiHa cells and appeared to protect CaSki cells from apoptosis (Ruutu et al., 2006). In human studies, it has been demonstrated that HR-HPV positive women had significantly higher morning and daily estradiol levels compared to HR-HPV negative women (Fischer et al., 2022). Estrogen receptors (ER) have been identified in epidermal keratinocytes and dermal fibroblasts of the vulva, which opens up the possibility that there may be an estrogen effect inducing oncogenic HPV activity on the vulva (MacLean et al., 1990). Ultimately, there should be further investigation into what specific characteristics of pregnancy, whether it be the unique gestational hormonal milieu, or other, could contribute to possible increased oncogenic effects.

According to the fifth edition of the World Health Organization Classification of Tumours of the Female Genital Tract, vulvar neoplasms are classified as either HPV-associated carcinomas or HPV-independent carcinomas (Höhn et al., 2020). We conducted a literature review by searching PubMed for case reports or case series of vulvar SC using the terms “sebaceous carcinoma” AND “vulva” AND “HPV” on April 13, 2023. We reviewed the relevant literature as well as articles cited in extracted papers. The two case reports of vulvar SC with HPV association were identified and are listed below in Table 1.

In the vulva, malignant neoplasms commonly include vulvar squamous cell carcinoma (vSCC), often with associated usual vulvar intraepithelial neoplasia (uVIN), which are induced by oncogenic high-risk HPV strains, including types 16 and 18. The present case discusses another malignant neoplasia, vSC. To compare patterns of invasion of the two malignant neoplasms, uVIN/vSCC tend to have infiltrative or pushing borders commonly with paradoxical maturation and/or desmoplastic stromal reaction, whereas vSC tend to grow in larger nests and be difficult to distinguish from benign sebaceous lesions. Among vulvar sebaceous carcinoma, an HPV association is rare, with only three cases including the present case reported to date, confirmed by in-situ hybridization (ISH). Four cases were reported to have a negative HPV association, with three of them confirmed by combinations of immunohistochemistry, Southern blot hybridization, and PCR and one with unspecified HPV testing (Hamza et al., 2023). All other cases did not report on HPV status. This patient had a positive history of HPV, which may have played a role in her development of vulvar sebaceous carcinoma although a mechanism of action has not been described. Hamza et al. provides the first documentation of two patients with vulvar SC/carcinoma with sebaceous differentiation for whom HPV was a potential driver of the neoplasms. For this present case, it remains unclear what the true pathology is and it is appropriate to refer to it with the same umbrella term coined by Hamza et al., vulvar intraepithelial carcinoma with sebaceous differentiation.

Due to the rarity of these cases, the optimal management and treatment are not well established. Generally, for management of periocular or extraocular SC the primary aim is complete surgical excision with clear histological margins. Of the total 16 cases of vulvar sebaceous carcinoma documented, only two patients did not undergo some form of surgical excision. One such patient succumbed to the disease after failing chemotherapy and immunotherapy. The other was treated with fluorouracil due to poor surgical candidacy, but subsequent punch biopsy demonstrated persistent tumor pathology identical to initial vulvar lesion. In comparison, outcomes for patients undergoing surgical management for vulvar SC were generally superior (Hamza et al., 2023). While routine SLND is recommended in addition for periocular SC, it is not routinely performed for extraocular SC due to limited data and complications including lymphocyst formation, lymphedema, and cellulitis (Owen et al., 2019). However, the present case can be considered distinct from classic extraocular SC as it can be classified as a vulvar neoplasia, for which inguinofemoral lymphadenectomy is indicated (Meads et al., 2014). SLND of groin lymph nodes with clinical follow-up of SLN-negative cases has been shown to have favorable prognosis in patients with early-stage vulvar cancer (Sakae et al., 2016). Yamamoto et al. also discuss a case of vSC in which a patient underwent local excision with SLND and remained asymptomatic at 14 month follow-up with no signs of recurrence (Yamamoto et al., 2021). With consideration of current recommendations following SLND in vulvar cancer, our current patient has been following-up at close intervals and remains without clinical signs of disease recurrence nine months after initial excision (Meads et al., 2014).

Regarding Muir-Torre syndrome (MTS), which is frequently associated with all variants of SC, pathology findings showed no loss of expression of MMR proteins including *MSH2*, *MSH6*, *MLH1*, and *PMS2*. Our patient also garnered a score of one on the Mayo Muir-Torre syndrome risk calculator, indicating no need for Lynch syndrome evaluation and further decreasing concern for MTS (Roberts et al., 2014). Ultimately the lack of consensus on the final pathology did not change management of the patient and the preferred treatment modality remained surgical excision.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Credit authorship contribution statement

Irena Kuan: Conceptualization, Investigation, Writing – original draft, Visualization. **Katherine Tian:** Conceptualization, Investigation,

Writing – original draft, Visualization. **Shannon Grabosch:** Conceptualization, Writing – review & editing. **Jennifer Sehn:** Conceptualization, Writing – review & editing. **John Hoff:** Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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