CASE REPORT

Vulvar eccrine porocarcinoma: report of a case and literature review

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Abstract

Adnexal carcinomas of the vulva are rare tumors. A case of an 83-year-old woman with a 3.5 cm vulvar lobulated mass that grew over an 18-month period is reported. Histopathological examination of the initial biopsy revealed a poorly differentiated infiltrating carcinoma. Treatment included radical vulvectomy with bilateral inguinal lymphadenectomy. The histological examination of the vulvectomy specimen resulted in eccrine porocarcinoma (EPC) diagnosis. A review of the literature disclosed eight vulvar cases previously reported. The study of the nine cases including the present revealed that the ages of the patients ranged from 32 to 88 years, with a mean of 66.1 years. The location of the tumor was most common in the labium majus. The size ranged from 2 cm to 5 cm (mean 3.3 cm). A longstanding history suggested that at least two (22.2%) tumors arose from a preexistent benign eccrine poroma. Considering the reduced prevalence of EPC, the diagnosis of this type of tumor is challenging. The follow-up varied from six to 132 months (mean 35.2 months). Two (22.2%) tumors recurred, three (33.3%) patients developed regional lymph node metastases, and two (22.5%) patients showed distant metastases. Only one patient died of the disease, two patients remained alive with tumor, and four (44.4%) patients showed no evidence of disease. Although a rare entity, EPC should be considered in the differential diagnosis of a vulvar mass. In the vulva, it is difficult to establish the clinicopathological predictors of prognosis of EPC. However, the markers of aggressiveness at extragenital sites may also apply to this vulvar tumor.

Keywords: cutaneous adnexal tumor, immunohistochemistry, porocarcinoma, vulva.

Introduction

Malignant vulvar tumors are relatively uncommon, accounting for 3% to 5% of female genital tract malignancies. Approximately 90% of malignant vulvar tumors are squamous cell carcinomas [1]. On the other hand, adnexal carcinomas of the vulva are exceedingly rare, accounting for less than 0.1% of all vulvar carcinomas [2].

The skin and modified mucosal surfaces of the vulva contain apocrine and eccrine glands, anogenital mammary-like glands, and pilosebaceous units. The spectrum of adnexal vulvar tumors tends to reflect the relative frequency of these adnexal glandular elements [3]. Most of the adnexal neoplasms are benign (70%), with *hidradenoma papilliferum* being the most common, followed by syringoma. Malignant adnexal tumors comprise the remaining 30% of the cases. Primary extra-mammary Paget's disease is the most frequent (87.5%), sometimes with an invasive component (29%). Infrequent cases of basal cell carcinoma (4%) and sebaceous carcinoma (2%) have been reported. Only rarely cases of pilomatrix carcinoma, hidradenocarcinoma, eccrine carcinoma, apocrine carcinoma, spiradenocarcinoma, malignant chondroid syringoma, cilindrocarcinoma, adenoid cystic carcinoma, mucinous adenocarcinoma, and adenocarcinoma of mammary-like glands have been described [3].

Vulvar porocarcinoma is a rare adnexal tumor. In fact, in a 32-year study performed by an institution on vulvar adnexal lesions, no case of porocarcinoma was observed [3]. To the best of our knowledge, only eight cases of vulvar eccrine porocarcinoma (EPC) have been reported in the English-language literature to date [4–10].

We report a new rare case of vulvar EPC and review the main clinicopathological features of the disease by comparison of our diagnosis with all eight cases previously published in literature.

Case presentation

An 83-year-old nulligravid woman presented with the complaint of a slowly growing lump on her vulva. It had been present for about 18 months but recently began to enlarge. She had a past medical history of type 2 diabetes mellitus, dyslipidemia and osteopenia. Physical examination revealed a 3.5-cm firm lobulated mass with superficial ulceration involving both labia majus, around the clitoris, and the left labium minus. Vaginal, cervical, urethral orifice and perianal examination were normal. The patient underwent a workup that included magnetic resonance imaging (MRI), revealing that the lesion did not involve the vagina, urethra, anus or inguinal lymph nodes. No distant metastases were seen in the abdominopelvic echography. An incisional (small) biopsy of the lesion was diagnosed as poorly differentiated, infiltrating carcinoma. Later on, a radical vulvectomy with bilateral inguinal lymph node dissection was done.

The surgical specimen measured 7×6.5×3 cm and included the central part of the vulva. The right lymph-adenectomy comprised nine lymph nodes and the left lymphadenectomy five lymph nodes. The vulva showed

a cutaneous, 3.5×2.5×2 cm, firm, ulcerated, lobulated mass with a tan-gray cut surface. The lesion involved both labia majus (Figure 1), around the clitoris, and the left labium minus.
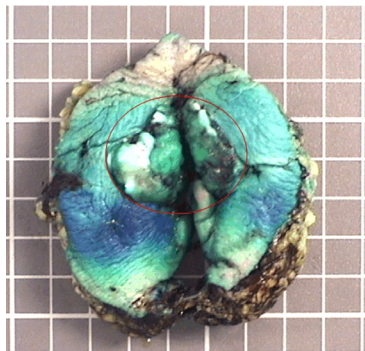

Figure 1 – *Gross picture of the vulvectomy specimen showing an ulcerated, 3.5 cm, multilobulated mass involving both labia majus and the left labium minus (ellipse). The external surface of the tumor was smooth. The specimen was colored in the surgical intervention.*

Microscopic study revealed that the mass consisted of lobules and broad interanastomosing trabeculae of variable size connected with the surface (Figure 2A). The cells were basaloid polyhedral, with mild to moderate atypia and pleomorphism. Nuclei were vesiculous, with visible nucleoli (Figure 2B). Lobules and trabeculae contained well-formed ducts lined by cuboidal epithelial cells often having an eosinophilic luminal cuticle. Less

well-developed ducts and cells showing intracytoplasmic lumina were present (Figure 2C). These cells were abundant in some fields (Figure 2D). Apocrine differentiation was not observed. Some areas displayed squamous differentiation with intercellular prickles and horn pearls (Figure 3A). Clear cell change was absent. Occasional areas showed melanin-containing spindle or dendritic cells in the lobules and in the stroma (Figure 3B). Melanin stained black with the Fontana–Masson method and remained unstained with the Perls' iron staining. The mitotic count was 16 mitoses per high-power field (HPF). The neoplasm had an infiltrative border (Figure 3C). Sometimes, the lobules showed comedonecrosis (Figure 3D). An *in situ* component of the tumor was not seen. Lymphovascular or perineural invasion was not observed. The tumor stroma was fibrous, with scant inflammatory cells. Using a calibrated ocular micrometer, the tumor depth invasion was 15 mm (*i.e.*, vertical distance from the erosive surface to the deepest point of invasion at the thickest region of the tumor). Surgical margins were free of tumor.

Immunohistochemical staining for carcinoembryonic antigen (CEA) demonstrated intercellular canaliculi formation (Figure 4A). Tumor cells showed positivity for cytokeratin (CK) 7 (Figure 4B), CK19 (Figure 4C), BerEP4, p16 (Figure 4D), p63 (Figure 5A), p53 (Figure 5B), and p40 (Figure 5C). These cells displayed negativity for androgen receptor and retinoblastoma binding protein-6. Staining for Ki67 labeled a high proportion (60%) of neoplastic cells (Figure 5D).
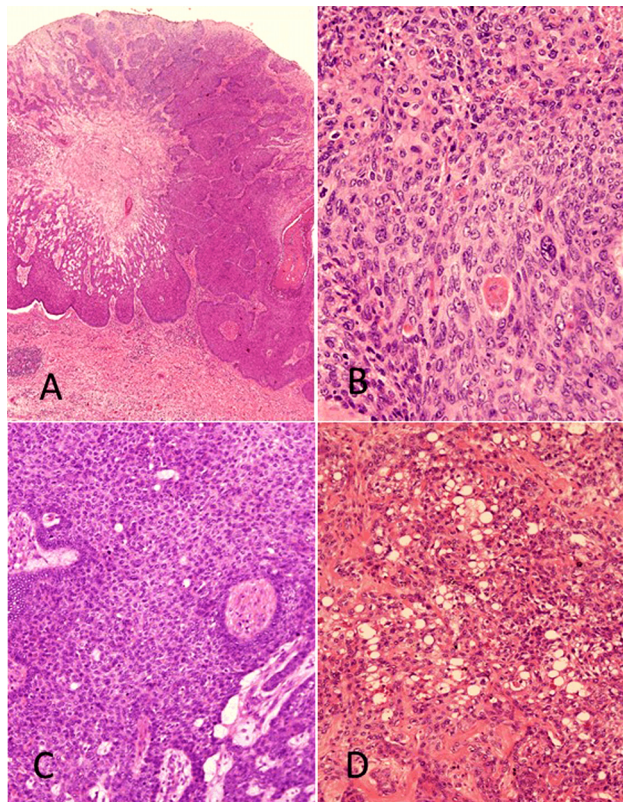

Figure 2 – *Histopathological study: (A) Ulcerated tumor composed of broad anastomosing trabeculae connected to the surface; (B) Cells show vesicular nuclei and visible nucleoli – cytological pleomorphism is evident; (C) Ductal differentiation; (D) Prominent intracytoplasmic lumina. Hematoxylin–Eosin (HE) staining: (A) ×40; (B) ×400; (C and D) ×200.*
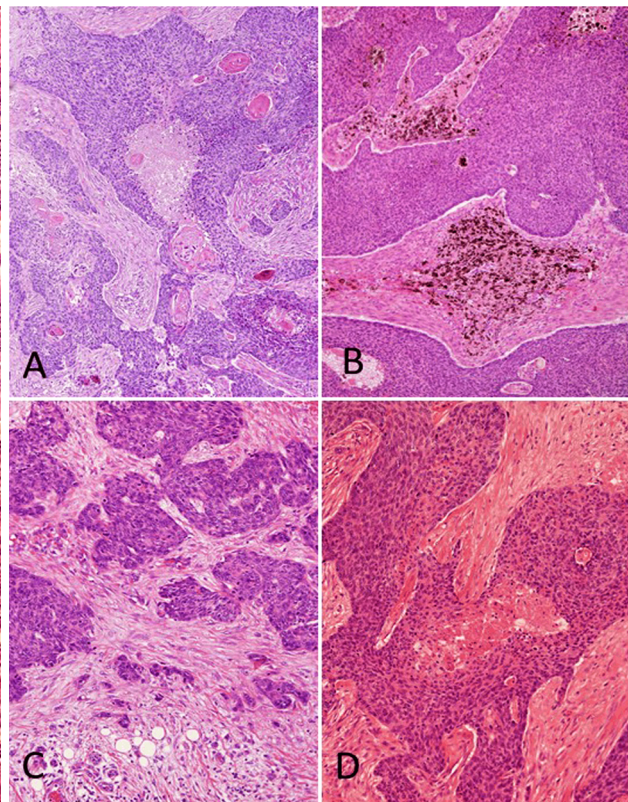

Figure 3 – *Additional histopathological study: (A) Squamous differentiation; (B) Melanin-containing spindle and dendritic cells within porocarcinoma trabeculae and in the stroma; (C) Infiltrative growth pattern; (D) Necrosis in the center of a trabecula. HE staining: (A and B) ×100; (C and D) ×200.*
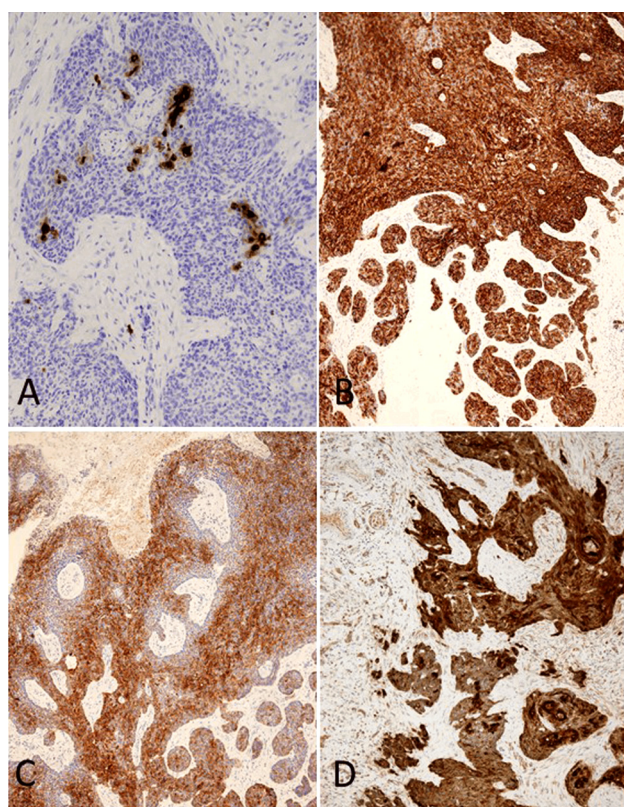
Figure 4 – *Immunohistochemical reactivity: (A) Ducts are highlighted by carcinoembryonic antigen (CEA) (Anti-CEA antibody immunostaining, ×200); (B) Cytokeratin (CK) 7 (Anti-CK7 antibody immunostaining, ×100); (C) CK19 (Anti-CK19 antibody immunostaining, ×100); (D) p16 (Anti-p16 antibody immunostaining, ×200).*

Figure 5 – *Immunohistochemical reactivity: (A) p63 (Anti-p63 antibody immunostaining, ×200); (B) p53 (Anti-p53 antibody immunostaining, ×200); (C) p40 (Anti-p40 antibody immunostaining, ×100); (D) Ki67 (Anti-Ki67 antibody immunostaining, ×200).*

Antibodies used in the immunohistochemical study are detailed in Table 1.

Table 1 – *Antibodies used in the immunohistochemical study*

Antibody	Source	Clone	Dilution	Retrieval solution pH (Dako)
CEA	Dako	II-7	FLEX RTU	High
CK7	Dako	OVTL12/30	FLEX RTU	High
CK19	Dako	RCK108	FLEX RTU	High
P40	Biocare Medical	BC28	1:50	High
BerEP4	Dako	Ber-EP4	FLEX RTU	High
P16	BD Biosciences	G175-405	1:50	High
P53	Dako	DO-7	FLEX RTU	High
P63	Dako	DAK-p63	FLEX RTU	High
Androgen receptor	Dako	AR441	1:50	High
Retinoblastoma binding protein-6	Abcam	Ab55787	1:100	High
Ki67	Dako	MIB1	FLEX RTU	Low

Abcam, Cambridge, UK; BD Biosciences, San Jose, CA, USA; Biocare Medical, Pacheco, CA, USA; CEA: Carcinoembryonic antigen; CK: Cytokeratin; Dako (Agilent Technologies, SL, Las Rozas, Madrid, Spain); RTU: Ready to use.
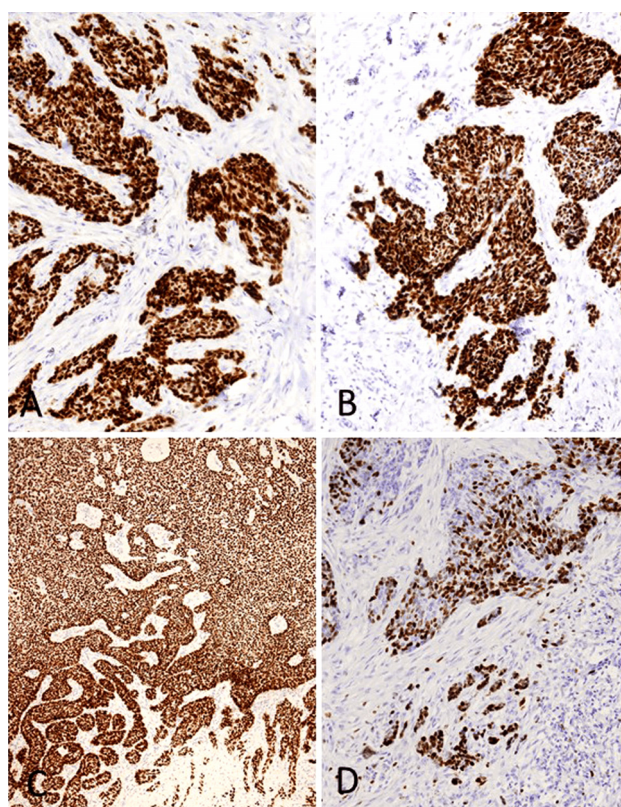
The study of inguinal lymph nodes revealed absence of tumor cells. The staging classification of the tumor was pT2, N0, M0 [stage II AJCC/UICC (*American Joint Committee on Cancer/Union for International Cancer Control*); stage II FIGO (*International Federation of Gynecology and Obstetrics*)].

The revision of the initial biopsy demonstrated that tumor was an EPC with presence of well-developed ducts.

She did not receive any adjuvant therapy. Twenty-six months after the radical operation, the patient was well and showed no evidence of recurrent disease.

⎆ Discussion

EPC is a very uncommon type of skin carcinoma thought to arise from cells of the acrosyringium. It represents 0.005% of all malignant epithelial tumors [11]. It is more common in elderly patients. Mean patient age is 77 years (range 43 to 99 years) [12]. The tumor is more frequent in females (60%) [13]. The lower extremity is the mostly involved region (44%). Other common sites are the trunk (24%) and head (18%) [13]. Clinical diagnosis is rarely made. It is a tumor without any particular clinical criteria to distinguish it from squamous cell carcinoma [12]. Diagnostic histological criteria include asymmetry, significant cytological atypia, and ductal differentiation or intracytoplasmic lumina [13]. Perineural or vascular invasion or infiltrative growth are not always present to assign a diagnosis of malignancy, but when one of them is present it is a sufficient indicator. Eccrine poroma can

progress from benign to malignant. This is supported clinically by long histories, mean 8.5 years, and recent onset of rapid growth in long-standing cases [14]. The ratio of malignant transformation from benign poroma to malignant one is about 18% [13]. Adverse prognostic factors include high number of mitoses (>14 mitoses per HPF), lymphovascular invasion, and depth of tumor invasion >7 mm [13]. In a study conducted by Robson *et al.*, the recurrence rate of the EPC was 17%, lymph node metastases appeared in 19%, and distal metastases or death were observed in 11% of patients [13]. An infiltrative tumor margin is strongly predictive of local recurrence [13, 15].

EPC of the vulva is an extremely uncommon lesion with only eight cases documented in the English literature [4–10]. The clinicopathological data of these eight previously described cases as well as our case are summarized in Table 2. These nine cases disclosed that the ages of the patients ranged from 32 to 88 years, with a mean and median of 66.1 and 75 years, respectively.

The location of the tumor was most common in the labium majus. The size ranged from 2 cm to 5 cm (mean 3.3 cm). In 44.4% of the cases, the initial diagnosis of the biopsy prior to the intervention was squamous cell or poorly differentiated carcinoma [7, 9]. Three (33.3%) cases, including ours, were initially diagnosed as poorly differentiated carcinoma, one of them as metastasis of unknown origin [7]. A longstanding history suggested that at least two (22.2%) tumors [5, 6] arose from a preexistent benign eccrine poroma. This rate is near to that described by Robson *et al.* [13]. Four (44.4%) cases, including ours, showed squamous differentiation [4, 6, 8] (Table 3). Melanin pigmentation in EPC is very uncommon [16]. In the present case, the pigmentation was focal, not clinically evident. Our case represents the unique EPC of the vulva showing (microscopic) pigmentation. Most reports do not include complete histopathological evaluable data, such as mitotic index, presence of lymphovascular invasion, tumor depth, and characteristics of the tumor margin (pushing or infiltrating) (Table 3).

Table 2 – *Summary of clinical details of cases reported as vulvar eccrine porocarcinoma*

Case No./ Reference	Age [years]	Location/ Maximum size [cm]	Time before diagnosis	Treatment	Recurrences/ Metastases	Follow-up/ outcome
1/[4]	80	Vulvar skin/NA	Several years	Excision + POR	3/0	48 mo/DUD
2/[5]	75	Left labium majus/3	15 years	Radical hemivulvectomy, bilateral lymphadenectomy + POR	0/6 of 15 left inguinofemoral lymph nodes	19 mo/NED
3/[6]	88	Right labium majus/3	>20 years	Simple local excision	0/0	6 mo/NED
4/[7]	32	Mons pubis-labium majus/4.5	NA	Excision + POR and chemotherapy	0/inguinal, retroperitoneal, and peribronchial lymph nodes, growth around vena cava, lung	10 mo/AWM
5/[7]	60	Right labium majus/3	NA	Excision, chemotherapy + POR	2/Iliac lymph nodes	132 mo/AWR
6/[8]	48	Left labium majus/5	5 months	Wide local excision, left inguinal lymphadenectomy	0/0	29 mo/NED
7/[9]	54	Vaginal vestibule/3.1	2 months	Local excision, bilateral inguinal lymphadenectomy + POR + chemotherapy	0/sacrum and both lungs	12 mo/DOD
8/[10]	75	Left vulvar two lesions/ 3 and 2	2 years	Radical vulvectomy, bilateral inguinofemoral lymphadenectomy + POR	0/regional lymph nodes	NA/NA
9/Present report	83	Both labia majus, around clitoris, left labium minus/3.5	18 months	Radical vulvectomy, bilateral inguinal lymphadenectomy	0/0	26 mo/NED

AWM: Alive with metastases; AWR: Alive with recurrent tumor; DOD: Death of disease; DUD: Death due to unrelated disease; mo: Months; NA: Not available; NED: No evidence of disease; POR: Postoperative radiation.

Table 3 – *Histological features of cases reported as vulvar eccrine porocarcinoma*

Case No./ Reference	Initial diagnosis	Tumor margin	Tumor depth [mm]	Mitoses	Lymphovascular invasion
1/[4]	Eccrine porocarcinoma	NA	NA	NA	NA
2/[5]	Eccrine porocarcinoma	Infiltrative	NA	Abundant	Present
3/[6]	Eccrine porocarcinoma	NA	NA	NA	NA
4/[7]	Poorly differentiated carcinoma, most likely metastatic	NA	NA	NA	Present
5/[7]	Undifferentiated carcinoma	NA	NA	NA	Present
6/[8]	Eccrine porocarcinoma	Pushing	8	6/10 HPF	Absent
7/[9]	Squamous cell carcinoma	NA	>20	NA	Present
8/[10]	Eccrine porocarcinoma	NA	NA	Abundant	NA
9/Present report	Poorly differentiated carcinoma	Infiltrative	15	16/10 HPF	Absent

HPF: High-power field; NA: Not available.

Current immunohistochemical markers of diagnostic utility for the diagnosis of vulvar EPC include CK7, CK19, BerEP4, p40, p53, p63 [17–20], Ki67, and androgen receptor. Overexpression of p16 protein and

loss of retinoblastoma protein reactivity can be used as useful markers of EPC to differentiate it from benign poroma [21]. Porocarcinomas are composed of two cell types including poroid and cuticular, while the other entities in the differential diagnosis are composed of a single cell type. In our case, there was no evidence of apocrine differentiation with ordinary staining. In addition, the androgen receptor was negative. The cuticular cells were demonstrated with CEA. The poroid cells were basaloid with no endocrine or melanocytic appearance. The patient was postmenopausal, with no apparent hormonal imbalance. Therefore, neuroendocrine and melanocytic markers and estrogen and progesterone receptors were not used.

Only 33.3% of cases were treated with radical surgery (Table 2). The follow-up varied from six to 132 months (mean, 35.2 months; median, 22.5 months). Two (22.2%) tumors recurred, three (33.3%) patients developed regional lymph node metastases [5, 7, 10], and two (22.5%) patients showed distant metastases [7, 9]. Only one patient died of the disease, two patients remained alive with tumor, and four (44.4%) patients showed no evidence of disease (Table 2).

Vulvar EPC is mainly found in patients of advanced age. The presentation is variable. Most cases arise *de novo*. The tumor requires a very high index of suspicion for its diagnosis. It is a rare neoplasm with potentially aggressive clinical behavior.

Our case displayed three of the four adverse prognostic factors established by Robson *et al.* [13], such as depth of invasion greater than 7 mm, more than 14 mitoses per 10 HPFs, and infiltrative growth pattern; however, the outcome was favorable. A short period of follow-up observation might be responsible for the inconsistency of the prognostic results.

The main differential diagnoses include conventional squamous cell carcinoma, basaloid squamous cell carcinoma, basal cell carcinoma, hidradenocarcinoma, melanoma, and skin metastases of different types of carcinoma.

EPC can show extensive squamous differentiation [22]. Although the appearances in these cases can be reminiscent of an invasive conventional squamous cell carcinoma, careful examination reveals the existence of true cuticle-lined ductal structures bordered by tumor cells, as well as frequent intracytoplasmic lumina within the tumor cells. These structures are highlighted with antibodies to CEA, confirming acrosyringial differentiation. CK19 is a powerful marker in distinguishing EPC (positive) from squamous cell carcinoma (negative). Other useful markers are CK7 and nestin [17].

EPC can also simulate basaloid squamous cell carcinoma and basal cell carcinoma [23, 24]. Basaloid squamous cell carcinoma is a bimorphic variant of squamous cell carcinoma, with basaloid and a squamous cell component that can be keratinizing. Wain's criteria include peripheral palisading of the tumor islands, intimate association with squamous cell carcinoma, small cystic spaces containing mucin, high nuclear-cytoplasmic ratio, high mitotic rate, solid growth, and prominent hyalinosis [25]. Anti-34-*β*-E12, and CK5/6 positive staining, and absence of neuroendocrine markers are mandatory for the diagnosis [26].

Basal cell carcinoma shows uniform cells resembling epidermal basal cells. These cells form nests with palisading of the cells at the periphery and haphazard arrangement in the centers of the nests. The stroma is fibromyxoid, with cleft artifact occurring between tumor nests and surrounding stroma because of shrinkage of mucin during fixation and staining. Tumor cells present reactivity for bcl-2 and BerEP4 and may show positivity for smooth muscle actin [27].

Hidradenocarcinoma may show overlapping features with EPC, especially if the latter is rich in clear cells. Hidradenocarcinoma is an intradermal tumor without epidermal connection, unlike porocarcinoma [28].

Cases of pigmented EPC have been diagnosed as malignant melanoma clinically [29] and histopathologically [30, 31]. Thus, non-neoplastic dendritic melanocytes may proliferate symbiotically with the porocarcinoma cells, not only in the primary skin lesion but also in metastatic foci. However, in these cases, the atypical cells express keratin and show ductal differentiation with CEA.

A cutaneous metastasis to skin from breast, lung, and other sites may simulate an EPC. The clinical data, the diagnostic features of EPC, the existence of an *in situ* component, and the selection of an immunohistochemistry panel are helpful to reach the correct diagnosis. In the selected panel, the inclusion of p63, CK15, and D2-40 improves diagnostic sensitivity and specificity [32].

Diverse histopathological features that are somewhat similar to other skin tumors can lead to misdiagnosis of EPC. Duct-like structures may be present but are typically absent in poorly differentiated tumors. Thus, incorrect diagnosis may result in inappropriate treatment and unfavorable outcome.

⊟ Conclusions

EPC of the vulva is a tumor without any precise macroscopic criteria to distinguish it from squamous cell carcinoma. Due to the rarity and non-specific clinical features of this tumor, it often presents a diagnostic challenge to clinical and pathologists. Although a rare entity, EPC should be considered in the differential diagnosis of a vulvar mass. EPC is uncommonly diagnosed preoperatively; thus, surgical management is usually not initially planned. This tumor may be misdiagnosed because of its rarity and heterogeneous histological appearance, with the consequent error in the choice of treatment that can lead to an unfavorable outcome. Considering there are only nine cases in literature, including this case report, it is difficult to establish the clinicopathological predictors of prognosis of vulvar EPC. However, the markers of aggressiveness at extragenital sites may also apply to vulvar EPC. In our case, the amplitude of surgical margins, the absence of lymphovascular invasion, and the absence of metastasis both in lymph nodes and visceral organs are favorable prognostic data. If the tumor is treated in a localized stage, radical surgery can be curative.

Conflict of interests
The authors declare that they have no conflict of interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

Ethics approval and consent to participate

No Ethics Committee approval is required in our Institution for a case report involving a single patient.

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