Case Report

Vulvar neuroendocrine carcinoma: a case report and literature review

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Background: Vulvar neuroendocrine neoplasms are extremely rare and reported only in case reports. Diagnosis and treatment are difficult because of the rarity of these tumors. This report describes a rare case of vulvar neuroendocrine carcinoma (NEC) and reviews the available literature on neuroendocrine neoplasms of the vulva to inform the clinical management of this rare tumor. Compared with similar cases that also with vulvar NEC, our patient received only vulvar wide local excision with no postoperative therapy and had good outcome until the next 17 months follow-up time.

Case Description: A 47-year-old woman presented to a local hospital with a 1-month history of a vulvar mass that had progressively enlarged over the preceding 2 months. She underwent vulvar wide local excision at the hospital. The pathological results showed high-grade NEC. The patient then sought treatment at our hospital. We performed vulvar wide local excision. The second pathological examination showed no residual tumor. The patient did not receive any postoperative therapy and was alive with no recurrence 17 months after the surgery. We describe the clinical characteristics of the 29 cases identified in the literature using a PubMed search.

Conclusions: In summary, vulvar NEC is a rare disease. Our case and the reviewed cases further our understanding of the clinical presentation, diagnosis, and treatment of this rare disease. Due to the limited number of available studies with a sufficient follow-up period and large patient sample, more cases should be included in the future to help establish new treatment guidelines.

Keywords: Neuroendocrine carcinoma (NEC); neuroendocrine neoplasia; vulva; review; case report

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Introduction

Neuroendocrine neoplasms are rare diseases of the female genital tract. The most common type of neuroendocrine neoplasm of the female genital tract arises from the ovary and is a clinically benign carcinoid tumor. Neuroendocrine neoplasms of the vulva are extremely rare and have been reported only in case reports. Therefore, it presents a diagnostic challenge, and there is no consensus regarding their optimal treatment because of the rarity of reported cases. The World Health Organization (WHO) 2014 classification divides neuroendocrine neoplasms of the genital tract according to the tumor site and grade [low-grade neuroendocrine tumor (NET) and high-grade neuroendocrine carcinoma (NEC)] (1,2). High-grade neuroendocrine tumors of the vulva include small cell NEC, large cell NEC, and Merkel cell carcinoma (MCC). The revised 2020 WHO classification divides neuroendocrine neoplasms into NET, small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC), and carcinoma admixed with NEC (3). Our report describes a rare case of vulvar NEC and reviews the available literature on neuroendocrine neoplasms of the vulva to inform the clinical management of this rare

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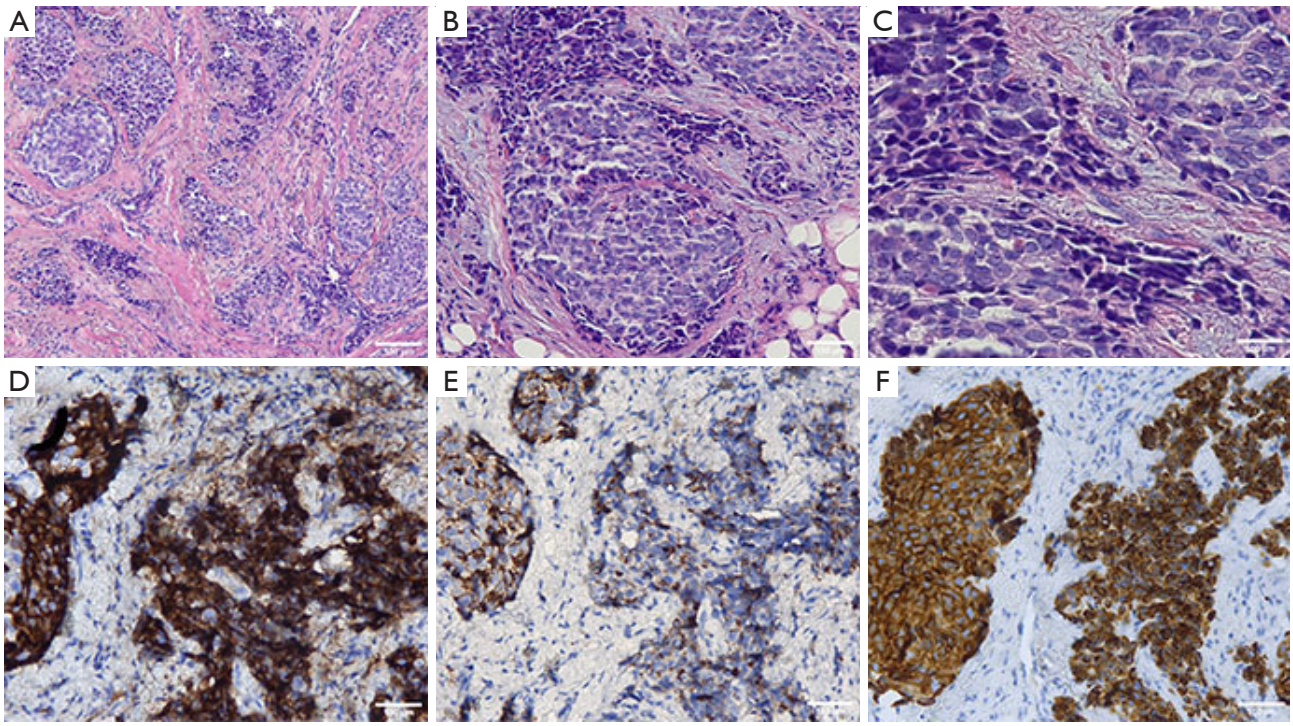

Figure 1 Histologic characteristics of vulvar neuroendocrine carcinoma. (A) Low-power view showing tumor cells arranged in sheets, nested, and cordspatternswithscanty cytoplasm (×100, H&E). (B,C) High-power view showing small tumor cells have hyperchromatic nuclei with finely stippled chromatin, indistinct nucleoli, and high nuclear to cytoplasmic ratio (B: ×200, C: ×400, H&E). (D-F) Immunohistochemical stains show diffused positive immunoreactivity for synaptophysin (D: ×200), partially immunoreactivity with chromogranin (E: ×200) and positive for P-CK of the tumor cells (F: ×200).

tumor. Compared with similar cases that also with vulvar neuroendocrine carcinoma, our patient received only vulvar wide local excision with no postoperative therapy and had good outcome until the next 17 months follow-up time. We present the following case in accordance with the CARE reporting checklist (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-62/rc).

Case presentation

A 47-year-old woman presented to a local hospital with a 2-month history of a progressively enlarging vulvar mass in the left labium majus without purulent discharge. The patient's previous medical history was normal. She first noticed the mass approximately 1 month prior in October, 2020 and sought treatment at a local hospital, where she underwent vulvar mass excision. The tumor was 1cm in diameter. Microscopically, the tumor was composed of sheets, nests, and cords of closely packed, oval to spindle, small cells with scanty cytoplasm (*Figure 1A*). The tumor cells have hyperchromatic nuclei with finely stippled chromatin, indistinct nucleoli, and a high nuclear to cytoplasmic ratio (*Figure 1B,1C*). Immunohistologically, tumor cells were positive for synaptophysin (*Figure 1D*), chromogranin (*Figure 1E*), and P-CK (*Figure 1F*), negative for CD56, HMB45, Melan-A, LCA. The pathological report was high-grade neuroendocrine carcinoma.

The patient then sought treatment at our hospital. Gynecological examination revealed swelling of the left labium majus and a scar from the previous excision surgery. A positron emission tomography and computed tomography (PET-CT) scan did not show any metastasis. Preoperative laboratory examinations were normal. We performed vulvar wide local excision on November 20th, 2020. The second pathological examination showed no residual tumor. The patient did not receive any postoperative therapy and was alive with no recurrence 17 months after the surgery. Pelvic and abdominal CT and lung CT showed no abnormalities in postoperative review till now. Close follow-up is still continued. All procedures performed in this study were in

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accordance with the ethical standards of the institutional and/or national research committee(s) (Number 2022026) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

Discussion

Neuroendocrine neoplasms arise in all sites of the female genital tract, including the cervix, endometrium, ovary, vagina, and vulva. Neuroendocrine neoplasms of the female genital tract are rare and comprise less than 2% of all genital malignancies (4). We searched the PubMed database for articles using the following search terms:"vulva" and "vulvar" combined with "neuroendocrine carcinoma", "MCC", "small cell carcinoma", and "neuroendocrine neoplasia". The included articles were limited to those published in the English language from the database's inception to February 2021. Twenty-nine cases were identified using the PubMed search.

Due to their rarity, neuroendocrine neoplasms of the genital tract present a diagnostic challenge for both gynecologists and pathologists, and the evidence is insufficient to implement universal treatment guidelines. *Table 1* presents the clinical characteristics of the 29 cases identified in the literature. There were 16 cases of MCC (5-20), five cases of neuroendocrine differentiation with other non-neuroendocrinecarcinoma (21-25), five cases of SCNEC (26-30), and three cases of non-specified type of neuroendocrine carcinoma (31-33). The time between the onset of symptoms and pathologic diagnosis ranged from 1 to 54 months. The age range at presentation was 28–92 years, and the average age was 57.2 years (*Table 2*). The mean tumor size was 4.2 cm (range, 1–9 cm). The labium majus, labium minus, Bartholin's gland, paraclitoral site, and the vulva (not specified) were involved in 15, 3, 5, 2, and 4 of 29 cases, respectively in *Table 2*. The clinical presentation of the neuroendocrine carcinoma was a local mass (75.9%), bleeding (6.9%), and pruritus (10.3%). Eight cases presented with inguinal metastasis. Because of the nonspecific symptoms, pathological findings are important for diagnosing neuroendocrine carcinoma of the vulva. The WHO 2020 classification describes the histological and chemical characteristics of the neuroendocrine neoplasms of the genital tract; histologically, NETs are characterized by a variable amount of cytoplasm and small nucleoli with uniform chromatin (3). SCNEC comprises highly atypical cells, scant to indiscernible cytoplasm, and ovoid to slightly spindled nuclei with hyperchromatic and dispersed chromatin (3). LCNEC is characterized by moderate amounts of cytoplasm and large nuclei with coarse chromatin (3). Dense cored secretory granules surrounded by limiting membranes are visible on electron microscopy (34). Immunohistochemical markers can also help differentiate neuroendocrine tumors. Synaptophysin, chromatin, and CD56 are the most commonly identified neuroendocrine markers (3). CK20 is typically positive for MCC, and CK7 and TTF are typically negative, ruling out neuroendocrine metastatic carcinoma (35). In addition to that, immunohistochemistry for neuron-specific enolase or argyrophil stains can help to differentiate neuroendocrine carcinoma from other small cell carcinomas of the vulva such as lymphoma, melanoma, poorly differentiated carcinoma of the Bartholin gland, and neuroblastoma (7). It is also important that patients undergo CT or PET/CT scans to rule out metastases from other sites such as the lungs or other genital female tract. According to the National Comprehensive Cancer Network (NCCN) guidelines, 26–36% of cases of MCC present with lymph node involvement and 6–16% present with distant metastasis (36). Our review found that the incidence of lymph node metastases at presentation was 28.6%. Therefore, PET-CT should be considered in these patients because of the high rate of metastatic spread.

Table 2 presents the treatment data for the included articles. The type of surgery, adjuvant therapy, outcome, and survival outcomes are presented in detail. Inguinal lymph node dissection was reported in 17 cases. Adjuvant therapy (including radiotherapy, chemotherapy, radiotherapy, and chemotherapy) was reported in 17 patients. The first line treatment for neuroendocrine carcinoma is surgical excision (35). The 2021 guidelines of the European Society of Gynaecological Oncology (ESGO) for vulvar cancers recommend radical local excision with <1 cm surgical free excision margins. For tumors >pT1a, groin treatment should be performed. Patients with unifocal tumors<4 cm in size with no suspicious groin nodes are suitable for the sentinel lymph node procedure (37). For patients with tumors of ≥4 cm and/or in cases of multifocal invasive disease, inguinofemoral lymphadenectomy is recommended (37). The 2018 NCCN Guidelines for MCC recommend wide local excision with 1–2 cm margins with sentinel lymph node biopsy (36). Unfortunately, there are no clear guidelines for treating neuroendocrine

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Table 1 The clinical features of patients in the included articles

Author, year	Age (year)	Size (cm)	Site	Clinical findings	Treatment	Histology	Follow up
Tang *et al.* 1982 (5)	67	1.5	The left labium minus	Intermittent burning of the vulva	Wide local excision + radiotherapy	Merkel cell carcinoma	2 years: left groin LN metastasis(mets); 27 months: neck and right proximal femur, liver mets; 30 months: died
Bottles *et al.* 1984 (6)	73	No	The left labia majora	Chronic ulceration	Drug administration + vulvectomy + left inguinal lymphadenectomy	Merkel cell carcinoma	9 months: local raised tumor + left inguinal LN mets 11 months:death due to acute MI + cardiopulmanary vessel mets
Copeland *et al.* 1985 (7)	59	6×8	The left labium majus	18- month history of a painful lump	Left hemivulvectomy and left inguinal lymphadenectomy + radiotherapy + vulvar lesion excision (8 months later)	Merkel cell carcinoma	8 months: pulmonary mets and 2.5 cm local mets; 12 months: died
Husseinzadeh *et al.* 1988 (8)	47	4.2×3	The right labium majus + vaginal introit	3-month history of right labial, groin swelling, vaginal discharge and pain + bilateral LN mets	Vulvectomy + bilaterallymphadenectomy + radiotherapy + local excision and chemotherapy (3 months later)	Merkel cell carcinoma	3 months: local and distant mets; 6 months: death
Chandeying 1989 (9)	28	4	The right labium majus	1-month history of a painless lump + right inguinal LN met	Radical vulvectomy and bilateral groin nodes dissection + radiotherapy	Merkel cell carcinoma	No follow up
Loret de Mola *et al.* 1993 (10)	28	3×2.5	The left paraclitoral	1-month history of local tumor	Local excision + wide local excisionand left inguinal lymphadenectomy (2 months later) + chemotherapy (8 months later)	Merkel cell carcinoma	8 months: liver mets; 20 months: death
Chen 1994 (11)	68	3×2.5	The left paraclitoral	1-month history of local tumor	local excision + chemotherapy (10 months later)	Merkel cell carcinoma	9 months: bilateral inguinal LN and liver mets; 17 months: death
Scurry *et al.* 1996 (12)	68	4×3	The Posterior fourchette and left labium minus	5-month history of a painless lump in the left side of the groin + bilateral inguinal met	Radical vulvectomy,bilateral inguinal node dissection, and left pelvic lymphadenectomy + chemotherapy and Radiotherapy	Merkel cell carcinoma	2 months: para-aortic lymph node mets; 5 months: Alive with Para- aortic met
Gil-Moreno *et al.* (13)	74	9	The labium majus	3 to 4 months history of a tumor in the labium majus	wide local excision	Merkel cell carcinoma	Free of disease at 13 months

Table 1 (*continued*)

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Table 1 (*continued*)

Author, year	Age (year)	Size	Site	Clinical findings	Treatment	Histology	Follow up
Fawzi *et al.* 1997 (14)	78	5.5×4	The right side of the vulva	1-month history of perineal itching and discomfort + pulmonary LN met	Radical vulvectomy with bilateral groin node dissection	Merkel cell carcinoma	20 days postoperative: died (right groin site broke down and died of bleeding)
Hierro *et al.* 2000 (15)	76	2.5	The left labium minus	A vulvar tumor of few weeks' evolution	local excision + local excision and left inguinal lymphadenectomy and radiotherapy(two months later)	Merkel cell carcinoma	2 months: local and nodal mets; 10 months: death
Pawar *et al.* 2005 (16)	35	6×4	The left labium majus	1 week history of Painful swelling of the vulvar and a purulent discharge + left inguinal LN met	The pus was drained + antibiotics + local excision	Merkel cell carcinoma	No follow up
Khoury-Collado *et al.* 2005 (17)	49	2	The right Bartholin's gland	Pain and swelling on the right side of the vulva	Radical wide local excision and bilateral inguinal lymph node dissection + radiothearpy	Merkel cell carcinoma	Alive at 2 years
Mohit *et al.* 2009 (18)	50	3–4	The left labia majus	3-month history of vulvar mass	local excision + radiotherapy and radical vulvectomy (2 months later) + chemotherapy (9 months later)	Merkel cell carcinoma	2 months: local recurrence mass; 11 months: death due to pulmonary embolism
Sheikh *et al.* 2010 (19)	63	5×7	The right labium majus	Bleeding and local mass	Wide local excision	Merkel cell carcinoma	2 months: local + distantmets + death
Iavazzo *et al.* 2011 (20)	63	9	The left labium majus	A lump of the left labium of the vulva + left LN met	Radical vulvectomy + radiotherapy	Merkel cell carcinoma	No follow up
Rahilly *et al.* 1995 (21)	69	4×3	The right labium majus	2-month history of vulvar itch and ulcerated swelling	Right hemivulvectomy	Mucinous adenocarcinoma with neuroendocrine differentiation	Alive at 2 years and 9 months with no recurrence
Graf *et al.* 1998 (22)	75	4.5×4	The left major labium	Genital bleeding	Radical vulvectomy with bilateral inguinal and femoral lymph lode dissection	Mucinous adenocarcinoma with neuroendocrine differentiation	Alive at four year follow up with no recurrence

Table 1 (*continued*)

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Table 1 (*continued*)

Author, year	Age (year)	Size	Site	Clinical findings	Treatment	Histology	Follow up
Zhang *et al.* 2012 (23)	40	3.5×2.7	The left vulva	3-month history of a painless left vulvar mass	Local excision	Solid papillary carcinoma with neuroendocrine differentiation	Alive at four year follow up with no recurrence
van Rosmalen *et al.* 2016 (24)	92	8	The left major labium	10-year history of a tumor progressively increased in size the last months	Partial vulvectomy and resection of the PET positive inguinal lymph node	Mucinous adenocarcinoma with neuroendocrine differentiation	Alive at 15 months with no recurrence
Gabrilovich *et al.* 2017 (25)	60	1.5 to 2	The right labia majora	2 to 3 months history of a small bump on her right vulva + LN met	Right radical wide local vulvar excision with right inguinofemoral lymph node dissection + radiotherapy + chemotherapy	Adenocarcinoma with neuroendocrine differentiation	Alive at 8 months with no recurrence
Jones *et al.* 1990 (26)	30	2	In the left Bartholin's gland	3-month history of progressively enlarging painful vaginal lump, dispareunia and left inguinal LN met	Local excision + diagnostic laparoscopy and inguinal node biopsy + chemotherapy	Small cell neuroendocrine carcinoma	No follow up
Cliby *et al.* 1991 (27)	35	Less than 1	The right hemivulva	2 months history of a vulvar mass	Right modified radical hemivulvectomy and bilateral superficial inguinal lymphadenectomy	Small cell neuroendocrine carcinoma	Alive at 21 months with no recurrence
Obermair *et al.* 2001 (28)	49	3.5×2	The right Bartholin's gland	5-month history of local swelling	Local excision	Small cell neuroendocrine carcinoma	Died 15 months, disseminated disease
Correia *et al.* 2017 (29)	70	No	Both labia	Gradual evolution pruritus gets worse	First:superficial vulvectomy; Then: radical vulvectomy and bilateral lymphadenectomy + right LN met)radiotherapy	High-grade small cell neuroendocrine carcinoma	No follow up
Jamshidi *et al.* 2020 (30)	53	4×2.1	The Bartholin's gland	Several weeks of pain at the vaginal	First: bartholinectomy; Then: wide radical vulvectomy and vaginectomy and sentinel lymphadenectomy + radiotherapy + chemotherapy + irinotecan and sterotactic body radiation (1 year later) + a left frontal craniotomy + whole-brain radiation (1 year later)	Small cell neuroendocrine carcinoma	1 years: liver mets; 3 years: brain mets

Table 1 (*continued*)

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Table 1 (*continued*)

Author, year	Age (year)	Size	Site	Clinical findings	Treatment	Histology	Follow up
Nuciforo *et al.* 2004 (31)	62	2	The right labia majora	Soft, painful lump	Local excision + radical vulvectomy and radiotherapy (three months later)	Neuroendocrine carcinoma	Three months :local recurrence and LN mets; Alive at 19 months with multiple abdominal and thoracic metastases
Aminimoghaddam *et al.* 2016 (32)	44	5×5	The left labium major	A mass in the vulva	Left hemivulvectomy and bilateral lymph node dissection	Neuroendocrine carcinoma	Alive at Four year follow up with no recurrence
Wu *et al.* 2018 (33)	56	3	At the left Bartholin's gland	1- month history of increasing pain and swelling with bleeding	Radical wide local excision and bilateral inguinal lymph node dissection and chemotherapy + hepatic lobectomy and chemotherapy (1 month later)	Neuroendocrine carcinoma	Alive at 6 months with no local and distant metastasis

LN, lymph node.

Table 2 The clinical findings and treatment of neuroendocrine carcinoma of the vulva

Characteristic	Number of the patients (%) or mean [range]
Mean age (years)	57.2 [28–92]
Mean tumor diameter (cm)	4.2 [1–9]
Location	
Labium minus	3 (10.3)
Labia majora	15 (51.7)
Bartholin's gland	5 (17.2)
Paraclitoral	2 (6.9)
Vulva (not specified)	4 (13.8)
Clinical presentation	
Local mass	22 (75.9)
Lymph node metastasis	8 (27.9)
Bleeding	2 (6.9)
pruritus	3 (10.3)
Ulceration	2 (6.9)
Intermittent burning	1 (3.4)
Surgical options	
Local excision	5 (17.2)
Wide local excision	7 (24.1)
Hemivulvectomy	3 (10.3)
Partial vulvectomy	1 (3.4)
Vulvectomy	2 (6.9)
Radical vulvectomy	11 (37.9)
Inguinofemoral lymph node dissection	
Yes	17 (58.6)
No	12 (41.4)
Ajuvant therapy	
Yes	17 (58.6)
Radiotherapy	8 (47.1)
Radiotherapy + chemotherapy	5 (29.4)
Chemotherapy	4 (23.5)
No	12 (41.4)

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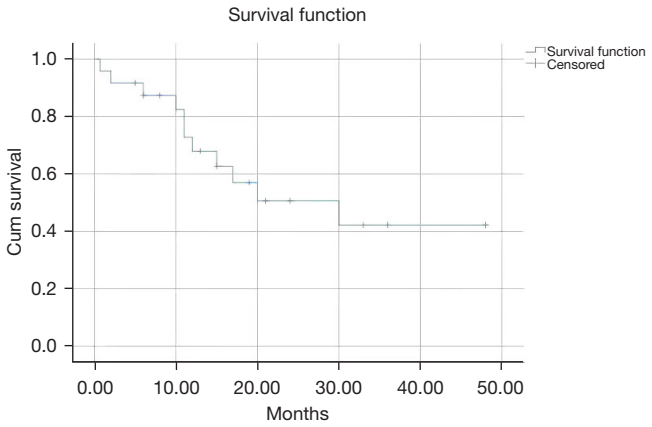

Figure 2 The Kaplan-Meier survival curve of the included 29 patients with vulvar neuroendocrine carcinoma

neoplasms of the vulva. The adjuvant radiation and/or chemotherapy is a reasonable consideration because of the aggressive performance of this disease in the vulva. *Figure 2* shows the Kaplan-Meier survival curve of 29 patients with vulvar neuroendocrine carcinoma included in the literature. The median survival time of included patients was 30 months. The 3-year survival rate was 42.2%. A total of 13/29 (46.4%) patients developed recurrence from 2–15 months; this was consistent with the recurrence of MCC, which has been reported to range from 25–50% (38). The 2018 NCCN Guidelines for MCC recommend wide excision without adjuvant therapy for cases with negative resection margins and no high-risk features. Otherwise, adjuvant radiation should be performed (36). The 2021 ESGO guidelines for vulvar cancer recommend postoperative radiotherapy in cases of invasive disease extending to or close to the pathological excision margins of the primary tumor, with>1 metastatic lymph node, and/or with extracapsular lymph node involvement (37).

The etiology of the neuroendocrine carcinoma was reported to be associated with old age, immunosuppression, European ancestry, and ultraviolet radiation (39). Genetic abnormalities were found in MCC cell lines, and less genomic aberration is associated with better survival (19). Mohit *et al.* reported that the MCC of the vulvar was more aggressive than that in other places (18). Postoperative monitoring is necessary for patients with neuroendocrine neoplasia. Approximately 9–19% of patients diagnosed with MCC subsequently developed another malignancy, and half of the patients experienced recurrence in the first three years (40,41). Close surveillance was recommended immediately after treatment, and PET/CT is useful in monitoring recurrence.

Our study demonstrates that wide local excision with negative margins may be sufficient for the treatment of the high-grade vulvar neuroendocrine carcinoma. This is not consistent with the high aggressive behavior of the disease in the previous reports. However, the data in our study regarding the disease is still limited to support the conclusion. An overview of the existing literature also helps clinicians understand the disease better.

Conclusions

In summary, vulvar neuroendocrine carcinoma is a rare disease. Our case and the reviewed cases further our understanding of the clinical presentation, diagnosis, and treatment of this rare disease. However, current studies include a limited number of cases and short follow-up; therefore, future studies with more cases are warranted to help establish new treatment guidelines.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-62/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gpm.amegroups.com/article/view/10.21037/gpm-21-62/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s)(Number 2022026) and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this

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