Southern African Journal of Gynaecological Oncology 2020; 12(1):1–5
https://doi.org/10.1080/20742835.2020.1740434

South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X

CASE REPORT

Advanced neuroendocrine carcinoma (Merkel cell carcinoma) of the vulva: a case report and literature review

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Neuroendocrine carcinomas (Merkel cell carcinomas) of the vulva are extremely rare tumours, with very few cases reported to date. Herein, a primary neuroendocrine carcinoma (Merkel cell carcinoma) of the vulva is reported. A 34-year-old HIV-positive female on antiretroviral therapy presented with a four-month history of a right-sided vulval mass. She underwent surgical excision of a histologically confirmed neuroendocrine carcinoma. Twenty-four weeks after surgery, she died. This case illustrates the importance of a broad differential diagnosis for neoplasms in the usual sites, and the aggressive nature of this tumour, which to date has had limited effective treatment options.

Keywords: Merkel cell carcinoma, neuroendocrine carcinoma, vulva, vulval carcinoma, vulvar carcinoma

Introduction

Neuroendocrine carcinoma (Merkel cell carcinoma) of the vulva is an extremely rare entity with fewer than 20 cases reported in the English literature to date.[1–18] Most cases show aggressive behaviour, with an almost universally reported poor outcome.[19] However, isolated reported cases have demonstrated better outcomes with complete surgical excision.[1] In sites other than the vulva, neuroendocrine carcinoma (Merkel cell carcinoma) of the skin is a rare and aggressive tumour predominantly affecting elderly persons, with purported pathogenetic mechanisms including ultraviolet light exposure[20] and polyomavirus infection.[21]

Herein, to the best of our knowledge, we present the first reported vulval neuroendocrine carcinoma in South Africa.

Informed consent was obtained from the patient, and ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), clearance certificate number M190494.

Case report

The patient was a 34-year-old HIV-positive female who was on antiretroviral therapy and had an undetectable viral load. She presented to the Gynaecologic Oncology unit at the Charlotte Maxeke Johannesburg Academic Hospital with a four-month history of a vulval mass, which was associated with a vaginal serous discharge. She also complained of pain at the site of the mass, with radiation to the right lower limb and back.

On clinical examination, there was a large fungating vulval mass measuring 6 × 3 cm, predominantly centred on the right labium majus, with involvement of the labium minus and clitoris centrally. There was no involvement of the urethra or vagina. There were palpable right inguinal lymph nodes that were clinically suspicious of involvement by the tumour. Abdominal ultrasound showed no evidence of intra-abdominal metastases and chest X-ray showed no evidence of a primary or metastatic lung tumour.

A radical vulvectomy with bilateral inguinal lymphadenectomy was performed. At surgery, it was suspected that the surgical margins were involved by tumour and that the inguinal lymph nodes may have been infiltrated by tumour. The tumour extended deep within the ischio-rectal fossae and there was deep para-vaginal extension. It was not possible to completely excise the tumour and as such there was residual tumour at the surgical margins. The specimen was submitted for histopathological assessment.

The specimen comprised an orientated vulvectomy measuring 100 × 60 × 50 mm, with surface skin measuring 100 × 40 mm. On sectioning, a solid tumour was identified involving the subcutaneous tissue, measuring 80 × 50 × 40 mm. The tumour was macroscopically clear of the skin excision margins; however, tumour was present at the mucosal excision margin. Sections were sampled from the tumour with overlying skin and mucosa, as well as the skin and mucosal excision margins.

Microscopically, the tumour was predominantly arranged in nests, with focal areas showing trabecular architecture (Figure 1). The nests were surrounded by thin fibrous septae and branching thin-walled capillaries. The tumour cells had moderate to scant, cleared to eosinophilic cytoplasm. The nuclei were round and had stippled chromatin. Nucleoli were indistinct. There were large areas of coagulative tumour necrosis. Up to 26 mitotic figures per 10 high-power fields were documented. The tumour involved 6 out of 11 inguinal lymph nodes in total. There was involvement of 4 lymph nodes on one side and 2 nodes on the other side. The laterality was not indicated on the respective specimen bottles.

A panel of immunohistochemical stains was performed. The tumour cells showed positive staining for synaptophysin, CD56, neuron specific enolase (NSE), C-KIT, MNF116, CAM 5.2

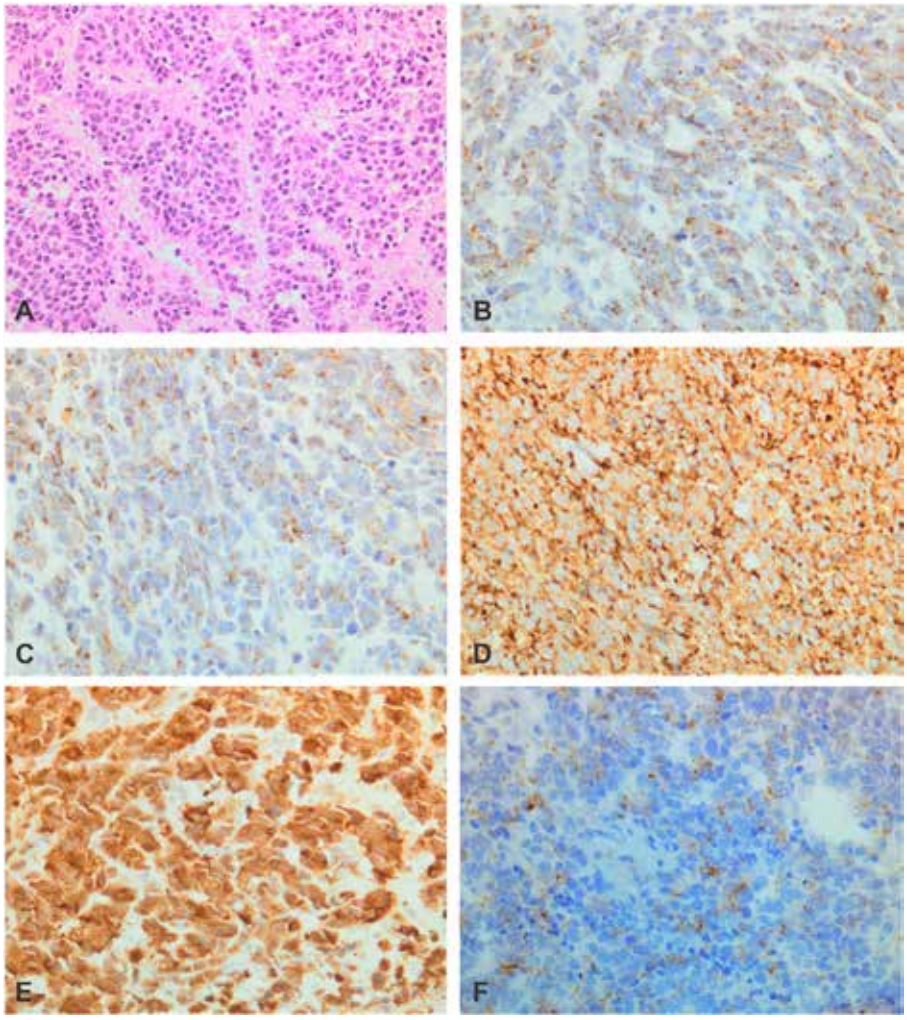

Figure 1: Microscopic images of the tumour and relevant immunohistochemical stains. (A) Haematoxylin and eosin stained section showing characteristic neuroendocrine morphology with nests of tumour cells with scant cytoplasm, clumped granular chromatin and nuclear moulding. (B) MNF116 immunohistochemistry stain showing positive dot-like staining in tumour cells. (C) CAM5.2 immunohistochemistry stain showing positive dot-like staining in tumour cells. (D) Synaptophysin immunohistochemistry stain showing diffuse positive cytoplasmic staining in tumour cells. (E) NSE immunohistochemistry stain showing diffuse positive cytoplasmic staining in tumour cells. (F) CK20 immunohistochemistry stain showing patchy positive staining in tumour cells. All images at 200x magnification.

and epithelial membrane antigen (EMA). There was focal CK20 staining identified (Figure 1). Chromogranin A was negative. A diagnosis of an invasive neuroendocrine carcinoma (Merkel cell carcinoma) was rendered.

The patient had an uneventful immediate postoperative course and was discharged from hospital 13 days following surgery.

At the second follow-up appointment eight weeks following surgery, tumour recurrence was suspected clinically and was confirmed on a CT scan. The CT scan showed features of a recurrent vulval mass with local extension to the vagina, cervix, uterus, anal canal, mesorectal fascia, right levator ani muscle, regional lymph nodes and distant bone metastases (in which there were multilevel vertebral lesions involving the thoracic and lumbar spines, with sternal involvement).

The patient was counselled and offered adjuvant chemoradiotherapy treatment. Unfortunately, she subsequently defaulted therapy and relocated to another province. Her family confirmed that she had died 24 weeks after her surgery.

Discussion

To date, 18 cases of neuroendocrine carcinoma of the vulva have been described in the English literature,[1–18] as well as 2 cases of neuroendocrine carcinoma of Bartholin's gland.[22,23] A recent systematic review on the subject by Nguyen *et al.*[19] (in 2017) included 17 of these cases (16 cases of neuroendocrine carcinoma of the vulva and 1 case of neuroendocrine carcinoma of Bartholin's gland). Two further cases of neuroendocrine carcinoma of the vulva were documented by Aminimoghaddam *et al.*[1] in 2016 and Correia *et al.*[6] in 2017 (Table 1).

The age of the patient described in the present case report (34 years old) is far younger than the mean age reported in the systematic review by Nguyen *et al.*[19] of 59.6 (28–79) years old; however, two of the cases in their series were younger than 30 years of age (both 28 years old).

The rapid appearance of recurrent disease (eight weeks after surgery) is in keeping with the previous review which found recurrent disease in 64.7% of patients at a mean follow-up time of 4.7 months (range 2–9 months).[19] The survival period of 24 weeks after surgery is also consistent with previous

Table 1: Summary of clinical presentation, treatment and outcome of vulval Merkel cell carcinoma[a].

Case	Age	Site and size	Presentation	Treatment	Outcome and Survival
Aminimoghaddam *et al.*[1]	44	5 × 5 cm left labium majus	Enlarging painless mass for 3 months	Left hemi-vulvectomy and bilateral inguinal lymphadenectomy. No additional treatment modalities	4 years: alive with no recurrence, locoregional involvement or metastases at follow-up
Bottles *et al.*[2]	73	Left labium majus	Minute ulcer with chronic ulceration	Initial: testosterone and hydrocortisone cream to heal initial ulcer 10 months, 3 weeks: vulvectomy and left inguinal lymph node dissection	9 months: local raised, nodular, erythematous 3 × 2 cm tumour and left inguinal nodal metastases 11 months (11 days following operation): death due to acute myocardial infarction and cardiopulmonary failure Metastases were noted in the inguinal and para-aortic lymph nodes, as well as in bone, liver, pulmonary vessels
Chandeving *et al.*[3]	28	4 cm right labium majus	Painless mass present for 1 month. Localised tumour and bilateral inguinal nodal metastases	Initial: vulvectomy and bilateral lymph node dissection and radiotherapy	3 months: pain in the right leg improved following symptomatic treatment 4 months: alive; no subsequent follow-up
Chen [4]	68	Mass measuring 3.25 cm noted to the left of the clitoris	Mass present for 1 month. Localised tumour	Initial: local excision 10 months: chemotherapy	8 months: bilateral inguinal lymph nodes and liver metastases 9 months: vulva, scalp, bone and para-aortic lymph nodes 17 months: death
Correia *et al.*[6]	70	Pruritis with white plaques on both labia	Long-standing history of pruritis. Clinical features suggestive of high-grade squamous intraepithelial lesion of the vulva	Initial: superficial vulvectomy Subsequent radical vulvectomy and bilateral lymph node dissection with adjuvant radiation therapy	Not stated
Copeland *et al.*[5]	59	Mass on left labium majus, which measured 8 × 6 cm.	Painful mass present for 8 months. Local tumour and left inguinal nodal metastases	Initial: left hemi-vulvectomy, lymph node dissection and radiotherapy 8 months: excision of vulval mass	8 months: vulval mass and several pulmonary metastases 12 months: death
Fawzi *et al.*[7]	78	5.5 × 4 cm right-sided vulval mass	A 1-month history of perineal discomfort and pruritis Pulmonary lymph node metastases	Radical vulvectomy and bilateral inguinal lymph node dissection	20 days after surgery: breakdown of right side of vulva Death due to exsanguination. No autopsy was performed
Gil *et al.*[8]	74	9 cm mass on the right labium majus	Mass present for 3 to 4 months	Initial: wide local excision	Disease free at 13 months
Hierro *et al.*[9]	79	2.5 cm mass on the left labium majus	Localised tumour	Initial: local excision followed by radiotherapy at 2 months	Local recurrence and spread to regional lymph nodes 10 months: death
Husseinzadeh *et al.*[10]	47	4.2 × 3 cm right labium majus	A 3-month history of right labial swelling with brown vaginal discharge and bilateral groin swelling	Initial: vulvectomy and bilateral lymphadenopathy, with radiotherapy 3 months: excision and chemotherapy	3 months: right thigh nodule, forehead nodule, single nodular lesion in left hilar region 6 months: death; at autopsy hilar, lung, liver and pancreas metastases
Khoury *et al.*[23]	49	2 cm right vulval mass (Bartholin's gland tumour)	Spontaneous rupture of a Bartholin's gland abscess. Minimal induration at the site	Initial: abscess drainage with wide local excision, bilateral nodal dissection and radiation therapy	24 months: alive without recurrence of disease
Iavazzo *et al.*[11]	63	9 cm left labial mass	A 6-month history of pruritus treated with corticosteroid cream 5 cm inguinal nodal metastases	Initial: radical vulvectomy and radiotherapy	No follow-up
Loret de Mola *et al.*[12]	28	2 × 1.5 cm mass on the left fourchette	A 3-month history of a mass on the vulva. Localised tumour	Initial: local excision 2 months: wide local excision together with left inguinal lymph node dissection 8 months: chemotherapy	8 months: liver metastases. 20 months: death

(*Continued*)

Table 1: (*Continued*).

Case	Age	Site and size	Presentation	Treatment	Outcome and Survival
Mohit *et al.*[13]	50	3–4 cm mass on the left labium majus	Palpable mass present for 3 months	Initial: local excision 2 months: radiotherapy 2 months, 3 weeks: radical vulvectomy 9 months: chemotherapy	2 months: 12 × 10 cm recurrent mass which was ulcerated and bled 9 months: left hip pain 10 months: no evidence of metastases 11 months: death due to pulmonary embolism secondary to deep vein thrombosis
Nuciforo *et al.*[14]	62	2 cm mass of the right labium majus	Localised painful mass	Initial: local excision. 2 months: radical vulvectomy and radiotherapy	3 months: bilateral inguinal nodal metastases 11 months: abdominal and mediastinal lymph nodal spread 19 months: alive with several abdominal and thoracic metastases
Pawar *et al.*[15]	35	6 × 4 cm mass of left labium majus	A 1-week history of painful vulval swelling together with purulent discharge and a lymph node mass	Initial: drainage of abscess together with antibiotic treatment and partial excision	No follow-up. The patient planned to receive radiotherapy in her home country
Scurry *et al.*[16]	68	4 × 3 cm mass of the left labium minus and fourchette 4 × 3 cm	A 5-month history of painless mass with rapid growth in last 2 weeks. Localised tumour with a purple hue of the overlying skin together with bilateral inguinal nodal metastases	Initial: vulvectomy and bilateral inguinal and left pelvic lymph node dissection 2 months: radiotherapy	Residual pelvic nodes following treatment. 2 months: para-aortic lymph nodes involved 5 months: alive with residual disease
Sheikh *et al.*[17]	63	7 × 5 cm mass of the right labium majus	Post-menopausal bleeding with fungating primary mass	Initial: wide local excision	2 months: local and distant recurrence with bilateral firm inguinal lymph nodes Death before follow-up treatment
Winer *et al.*[18]	69	3–4 cm right inguinal mass	Inguinal mass noted by the patient	Initial: surgical excision Plans for adjuvant chemotherapy and radiotherapy	No follow-up
Wu *et al.*[22]	56	3 cm mass left labium majus (Bartholin's gland tumour)	Increasing pain and swelling left vulva with bleeding	Initial: wide local excision with bilateral inguinal lymphadenectomy with six courses of adjuvant chemotherapy 1 month: hepatic lobectomy with chemotherapy	1 month: liver metastasis Alive, recurrence and metastasis free, at last follow-up 6 months post-initial treatment

[a]Adapted from Nguyen *et al.*[19] (Clinical features and treatment of vulvar Merkel cell carcinoma: a systematic review. *Gynecologic oncology research and practice* 2017; 4: 2) under the Creative Commons Attribution 4.0 International License (available at http://creativecommons.org/licenses/by/4.0/), with the addition of three studies, Aminimoghaddam *et al.*[1], Correia *et al.*[6] and Wu *et al.*[22] in Table 1; rows 1, 5 and 20.

literature showing death at an average of 9.6 months after initial surgical operation.[19]

The pathogenesis of vulval neuroendocrine carcinomas has not been extensively studied. Studies of vulval and non-vulval Merkel cell carcinoma have suggested infection by a polyomavirus termed Merkel cell polyomavirus[13,21] [85] and UV light exposure[20] as pathogenetic mechanisms. The exact origin of Merkel cells has been a point of debate for many years, with recent suggestions of pre-B cell lymphoid origin, as demonstrated by a study of 21 cases by Jankowski *et al.*[24] of non-vulval Merkel cell carcinoma, which showed immunohistochemical staining for terminal deoxynucleotidyl transferase (TdT) and paired box protein 5 (PAX 5). Immunohistochemical cross-reactivity between PAX5, PAX2 and PAX8 expression has also been documented.[25] Whilst it may currently be too soon to suggest a B-cell origin of Merkel cell carcinoma, it is important to bear in mind that positive staining of TdT and PAX5 in Merkel cell carcinoma may be a diagnostic pitfall as these markers tend to be identified in B-cell lymphoblastic lymphomas/leukaemias.

None of the previously reviewed cases in the vulva were reported in HIV-positive patients. However, studies in non-vulval Merkel cell carcinoma have shown an 11-fold increased risk of Merkel cell carcinoma in HIV infection.[20] It is thus suggested that the patient's HIV status is an important risk factor for the development of this tumour.

The microscopic morphology and immunohistochemical profile are in keeping with most previous case reports that included immunohistochemistry results. However, the negative chromogranin is an important pitfall to note in this case. This emphasises the importance of the utilisation of immunohistochemistry panels to avoid the possibility of excluding an entity based upon a single negative immunohistochemical stain. It also emphasises the importance of light microscopic features on haematoxylin and eosin-stained sections, which in this case showed convincing neuroendocrine morphology throughout.

Surgical treatment is the primary treatment modality reported in the published cases reviewed, with some showing a role for adjuvant radiotherapy[11,13] and chemotherapy for metastatic

disease.[4,10–13] In addition, studies have shown significant PD-L1 expression and immunogenicity in Merkel cell carcinomas, particularly those associated with polyomavirus infection.[26] Following on from these findings, recent clinical trials have indicated promising results for the treatment of metastatic Merkel cell carcinoma with PD-1/PD-L1 checkpoint inhibitors.[27]

Conclusion

This case illustrates the importance of a broad differential diagnosis with regard to rarely occurring tumours in particular sites, and the appropriate immunohistochemical work-up thereof. In addition, the present case, as well as the literature reviewed, confirms the extremely poor prognosis associated with this condition in the vast majority of cases, highlighting the need for improved treatment approaches in the future. In this regard, PD-1/PD-L1 checkpoint inhibitor therapy for these tumours is a promising current area of research.

None of the previously reviewed case reports were noted to have been in HIV-positive patients, making this the first description in this group of patients, with the possibility of a pathogenetic relationship requiring further investigation.

The write-up of this case report will contribute to the scant literature currently available regarding Merkel cell carcinoma in this site and should assist with the gathering of information regarding future diagnosis, prognosis and treatment options in these tumours.

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Received: 4-12-2019 Accepted: 6-03-2020