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Case report on verrucous vulva carcinoma in an HIV-seropositive woman

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Abstract
Verrucous carcinoma of the Vulva is a rare[1] lesion affecting essentially postmenopausal women. The lesion is distinct and particular entity in vulval carcinoma classification and scalability is uncertain and unpredictable. Here, we present a 40 year old patient, who presented with a vulval mass of about 20 years duration that increased gradually in size. Patient is a known HIV positive patient on HAARTS that had multidisciplinary management and surgical excision. She has done well and is currently on follow-up.

Keywords: Verrucous vulva cancer, vulva neoplasia, giant vulvar warts, condylomata acuminate, vulva surgery

Introduction
Carcinoma of the vulva is an uncommon malignancy in women accounting for approximately 4 percent of gynaecologic neoplasms. Squamous cell cancers (SSC) account for about 90 percent of vulvar carcinoma cases [1]. Verrucous vulvar cancers are a rare subtype of SCC of the vulva. Often misdiagnosed as a Buschke-Lowenstein tumour (giant condylomata acuminata), verrucous vulva carcinoma is an aggressive locally invasive malignancy typically incapable of metastasis [2].
The aetiology of vulvar cancer is linked to the human papilloma virus infection in women of reproductive age; and chronic inflammation in post-menopausal women.[1] Other risk factors include: consumption of alcohol, cigarette smoking, family history of vulvar cancer, previous history of cervical dysplasia or carcinoma and co-morbidities such as granulomatous venereal disease and diabetes mellitus [1]. Although rarely associated with mortality, it causes significant morbidity and inconvenience to the patient.
Clinically, the patient presents with chronic vulvar irritation with associated pruritus and sanguineous discharge. Typically, there is no lymph node or bone involvement. Verrucous vulva carcinoma may be mistaken for giant condylomata acuminata but after poor response to management of the latter, the clinician should entertain the diagnosis of the former [3].
Like all malignancies, diagnosis is majorly histologic. The vulvar mass is often described as an indolent, exophytic, well-differentiated, low-grade squamous cell carcinoma with hyperkeratosis.
A search of available literature revealed a South-Western Nigeria study in which tumours in a tertiary hospital between 1981 and 2008 were retrospectively characterised [4]. Another study in Northern Nigeria assessed their archives from 2005 – 2015 to observe the pattern of vulvar cancers [5]. Both papers showed that vulvar cancers constituted 1.2% and 2.6% of all the gynaecologic cancers in both centres respectively, showing the rarity of this case in Nigeria [4, 5].
Here, we report a case of verrucous vulva carcinoma in a human immunodeficiency virus (HIV) seropositive woman.
The Case
A 40-year old HIV-positive primiparous unmarried Nigerian farmer presented in the Accident and Emergency unit with complaints of vulvar mass and discharge of 20 years' and 4 years' duration respectively. The lesions began as multiple pimple-sized growths in her vulva first detected over 20 years ago which gradually increased in size and coalesced to

to form a huge mass with smaller satellite masses. The masses were associated with pruritus, dyspareunia and later, pain which she scored 6 on a pain scale of 1-10 (with 1 being the least and 10 being the most conceivable pain). The pain is exacerbated by urination and relieved by washing the vulva with warm water. The increasing size associated pain necessitated seeking medical review.

The patient was initially reviewed at a local hospital in Kaduna five years prior to presentation where an excisional biopsy was attempted with no histology report. The wound started discharging serosanguinous fluid a few weeks post-excision biopsy. The discharge was malodorous, and initially scanty but later became more sanguineous and copious. Her re-presentation to the same hospital was met with a rebuff due to fear of further post-excisional bleeding, thus, she presented at our facility in 2021 for expert review and management.

She is a known HIV patient diagnosed in 2017 and commenced HAART a year later. The patient was initially started on first line regimen of antiretrovirals but is currently on second line regimen of Tenofovir/ Lamivudine/ Atazanavir/ritonavir following virologic failure.

No other co-morbidities, no family history of malignancies, no history of alcohol consumption, smoking or multiple sexual partners. She attained menarche at 15 years and coitarche at 18 years of age. The patient has treated genital tract infections before the onset of and during the current problem but she is unaware of the diagnoses. No previous history of pap smear test or contraceptive use. Her last normal menstrual period was a year prior to presentation; and she is the mother of a 22-year old lady who is now married.

In the general outpatient department of National Hospital Abuja, she was initially assessed and diagnosed with giant condylomata acuminata to rule out vulvar tumour. Following increasing intensity of pain despite the use of oral antibiotics and twice daily sitz bath, she was referred to the gynaecology department.

Examination revealed a young lady in painful distress, moderately pale, with a regular pulse rate of 80 beats per minute and normal blood pressure of 125/60mmHg. There was inguinal lymphadenopathy bilaterally. The introitus was occupied by a huge, cauliflower-shaped multinodular sessile masses coalesced into one measuring about 16cm x 8cm x 6cm. The mass obliterated the clitoris and both the labia majora and minora, extending toward the anal region and intergluteal cleft. There were several smaller fleshy masses surrounding the major mass which was bleeding and discharging malodorous serosanguinous fluid.

Speculum examination was deferred to avoid provoking further bleeding.

Examination of other systems was unremarkable

An initial diagnosis of genital warts to rule out vulvar cancer was made.

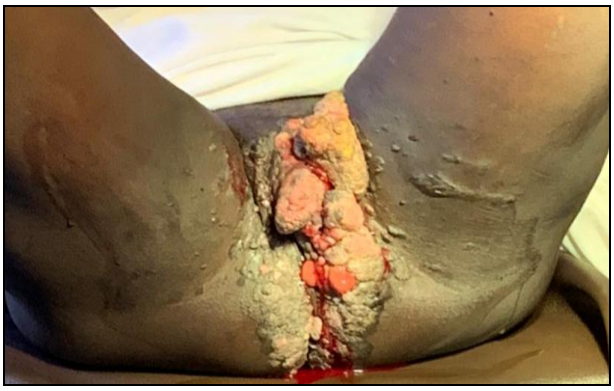

Fig 1: Cauliflower-like multinodular vulvar mass pre-operatively

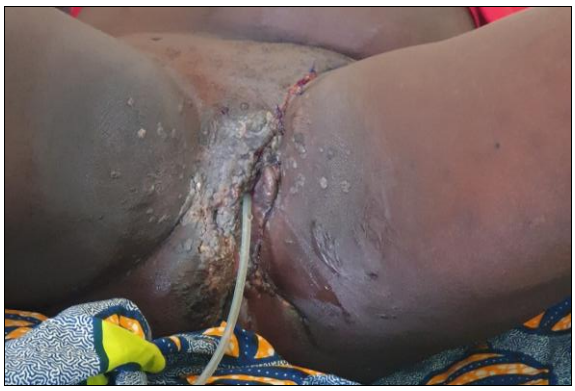

Fig 2: Healing vulva two days post-op with a urethral catheter *in situ*

Laboratory results

Complete blood count: Packed cell volume: 19% (40-54), Haemoglobin concentration: 6.5g/dL (13-18), WBC count: 5.9 x 10^5/L (4.8-10.8), Platelet count: 492 x 10^5/L (140-400)

Creatinine: 112umol/L (44-100)

Electrolytes, urea, liver function tests were within normal limits.

Serological tests for HBV, HCV and VDRL were all negative.

CD4 count: 783 cells/mm^3

Viral load: 30 copies/ml

Management

She was placed on twice daily sitz bath with warm saline, commenced on antibiotics (detailed below), transfused with a pint of whole blood and scheduled for surgical excision of the tumour. Due to the severe anaemia, the excision biopsy was expedited to prevent worsening of the anaemia.

Intraoperatively, she was transfused with 2 units whole blood and the multinodular mass was excised with a wide free margin while the smaller masses were cauterized. The excision biopsy was fixed in formalin and sent for histologic review. Estimated blood loss was one litre. Post-operatively, the patient was stable and she was prescribed parenteral ceftriaxone 1g b.i.d and metronidazole 500mg t.i.d for 48 hours.

On the second day after the surgery, her parenteral antibiotics of ceftriaxone and metronidazole were converted to oral cefuroxime 500mg b.i.d and metronidazole 400mg t.i.d; wound dressing was recommended twice daily with povidone iodine; and Vitamins B, C and E, haematinics, analgesics, and a strict protein diet were prescribed.

Histology report

Malignant epithelial tumour composed of well-differentiated squamous epithelial cell proliferation exhibiting papillomatosis and hyperkeratosis. Also seen are blunt

projections of the epithelium with deep bulbous processes and pushing margins. The composing cells are large and polygonal with abundant pink cytoplasm and enlarged nuclei with little nuclear atypia. Mitotic figures also noted. The subepidermal stroma consists of nests of malignant epithelial cells interspersed by fibrous tissue. The lymph nodes showed no features of malignancy.

A definitive diagnosis of verrucous carcinoma of the vulva was made.

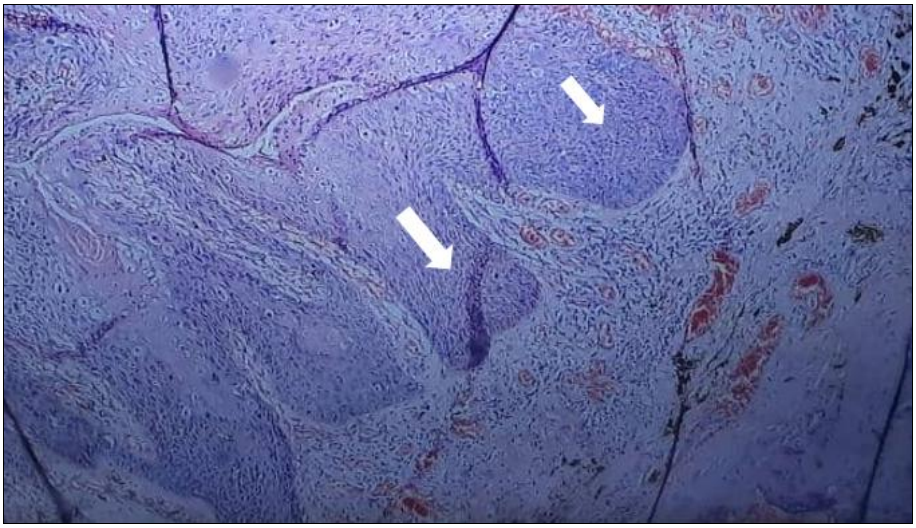

Fig 3: Tissue sections of the vulvar tumour with arrows showing blunt projections of the epithelium with deep bulbous processes, pushing margins and hyperpapillomatosis (H&E stain x 40)

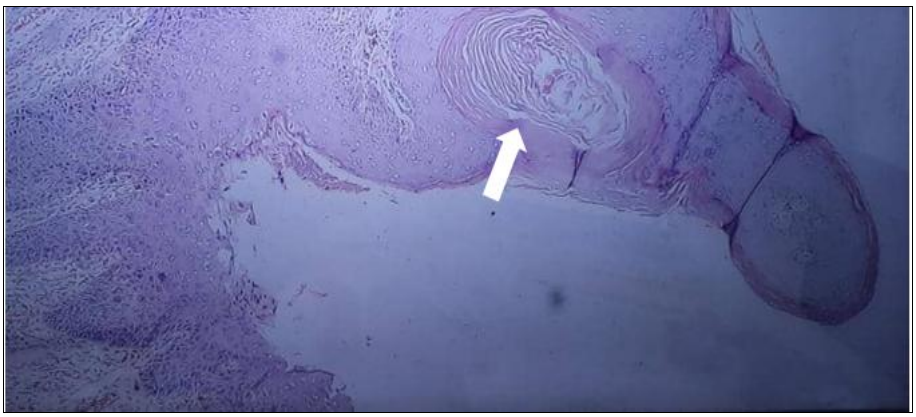

Fig 4: Tissue sections of the vulvar tumour showing hyperkeratosis (H&E stain x 40)

The patient was co-managed with oncologists and plastic surgeons for possible chemotherapy and reconstructive surgery respectively. The urologists and general surgeons were also invited post-operatively following wound dehiscence for possible diversion colostomy to encourage wound healing by secondary intention but this was eventually deemed unnecessary.

Due to the propensity for recurrence of this malignancy, the patient was followed up at 2-weekly intervals after discharge. The wound was granulating well seven weeks postoperatively after initial wound dehiscence one week after the surgery. Four months on, the patient is tumour-free.

Discussion

Vulvar carcinomas are often predominant among post-menopausal women. This patient does not fit into the usual age demographic for this malignancy however, this may be explained by the compromised immune status associated with HIV. HIV targets immune surveillance cells particularly the CD4+ cells which play a role in preventing the proliferation of malignant cells. Once the CD4+ cells have been compromised, cancer cells are harder to keep in check by few other cells such as the natural killer (NK) cells.

Excision biopsy is the specimen for definitive diagnosis and this must be taken to include the transition between the tumour margin and the normal vulvar tissue in order to aid appropriate diagnosis and prevent tumour recurrence. Histology report will aid in the grading of these cancers from I to III with grade I being the well-differentiated and grade III comprising poorly differentiated cells. As seen in this patient, the warty type of vulvar carcinoma is often associated with immunodeficiency and HPV infection in a younger demographic.

According to the Globocan database of 2018, human papilloma virus (HPV) is responsible for 31.4% of cancers worldwide [6]. HPV has been implicated in the development of vulva carcinoma particularly in premenopausal women with HIV. HPV is a 55nm-sized non-enveloped DNA-virus virus with an icosahedral capsid and double stranded circular genome. Spread through direct sexual contact, it typically alters squamous epithelium inducing neoplastic change particularly in the anogenital tract [7]. The presence of the virus interferes with DNA replication resulting in

DNA single strand breaks and mutations that facilitate tumourigenesis. Its low-risk types are associated with wart formation while the high-risk types are associated with neoplasia.

Verrucous carcinoma of the oral cavity was first documented by Ackerman in 1948 but Aird, *et al*. also described the squamous cell carcinoma-variant of the foot [8, 9]. Indeed, the verrucous carcinoma may not only affect the external genitalia but also the skin particularly the plantar surface of the foot, oesophagus, larynx, cervix, bladder, anus and other epithelium lined by keratinized or non-keratinized squamous cells. Due to its insidious nature, lack of cachexia and peripheral lymphadenopathy, it is often misdiagnosed as a Buschke-Lowenstein tumour refractory to treatment.

In a study involving patients with verrucous cancer of the anogenital region, HPV DNA was found in 83.3% of cases using in-situ hybridization [10]. Both low-risk and high-risk HPV types were detected which are easily preventable following administration of vaccines from childhood to early adulthood. However, in a study involving female undergraduate students in Nigeria, a very low vaccine uptake rate of 0.44% was observed with 5.2% of the students being aware of the human papilloma virus while less than a fifth of the respondents were aware of the existence of HPV vaccines [11].

Although an initial diagnosis of giant vulvar warts was made, this was discarded in favour of the histological diagnosis. This emphasizes the central role histologic examination plays in the diagnosis of vulvar carcinomas. Ideally, this should have been done prior to the excision surgery but the patient's anaemia from the bleeding masses precluded such management and the excisional biopsy was expedited to prevent further deterioration in the patient's haemodynamic status.

Management is primarily surgical. Maintaining a ≥ 1cm free surgical margin cannot be over-emphasized. Oftentimes, lymphadenectomy is not necessary as lymph nodes are rarely involved [12]. If the excision is extensive, grafts or flap may be necessary to restore cosmesis. Post-surgery, care must be taken to prevent surgical site infection which could delay wound healing and prolong hospital stay as occurred in the patient. Radiotherapy is discouraged because it can induce an anaplasia increasing metastatic risk. Preventive measures include education about safe sexual practices and encouraging the use of HPV vaccines to forestall HPV infections which will eventually increase the likelihood of malignancies in the female genital tract.

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Competing interests
The authors declare no conflicting interests

Ethical approval
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