Vulvar Squamous Cell Carcinoma in a Patient with AIDS: A Case Study

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Abstract Vulvar cancer comprises 5% of gynecological cancers with squamous cell carcinoma (SCC) being found in 90% of the cases. Vulvar intraepithelial neoplasia is human papilloma virus (HPV)-driven and is the precursor lesion in nearly 40% of all cases of vulvar SCC. Pruritus is reported as the most common initial manifestation of vulvar SCC which may be of a long duration with pain, discharge, and bleeding been less frequently reported which contributes to the delayed initial presentation of the disease. So far, there are no recommended screening strategies for vulvar cancer and HPV vaccination may be the only effective way for prevention. We present a case of advanced vulvar cancer in an immunocompromised host. We will review pertinent topics for the clinicians on HPV infection prevention, clinical course, staging and the need for strong efforts on patient education.

Keywords: *vulvar cancer, vulvar squamous cell carcinoma, HIV, AIDS, HPV*

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1. Case Presentation

A 44-year old woman with past medical history of squamous cell carcinoma of vulva, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) with history of poor medication adherence and multi drug resistant virus, ischial osteomyelitis and seizure disorder presented with complains of generalized weakness, fatigue, odynophagia, dysuria, bilateral upper thigh pain. described as constant 8 out of 10 aching pain with no radiation, no alleviating factor aggravates with movement, and inability to ambulate due to pain.

She denied chest pain, abdominal pain, dyspnea, dysuria, hematuria, nausea, vomiting, diarrhea, syncope and dizziness.

On admission, blood pressure was 96/65, heart rate 103, respiratory rate 19, oxygen saturation of 100% on room air, and temperature of 97.2 F, body mass index (BMI) 17.1 kg/m^2.

The patient appeared older for her age and cachectic. Bitemporal wasting, pallor and oral thrush were noted with normal heart, lung and abdominal exams. The pelvic exam revealed large erythematous fungating vulvar masses, fixed to the pubic bone with bilateral inguinal lymphadenopathy and occupying the entire surface the labia majora. The fungating vulvar lesion on the right was 4 x 10cms (Figure 1).

Figure 1. Vulvar lesion. (Photo taken with patient's permission)

Patient initial symptoms had started one-year prior to presentation, with a lesion appearing on the right labia majora, biopsy performed in another facility revealed high grade squamous cell carcinoma, keratinized and cervical Papanicolaou smear showed low-grade squamous intraepithelial lesion (LGSIL) with positive for Human papillary virus (HPV), however the patient declined

medical care. Over the months, patient developed anorexia and progressive weight loss with progressive enlargement of the labia majora lesion. Five months prior, she was found to have ischial osteomyelitis which was diagnosed as decreased T1 signal within the right ischium with peripheral enhancement on MRI (Figure 2), and treated at another facility. Patient was referred multiple times to GYN-Oncology but was lost to follow-up.
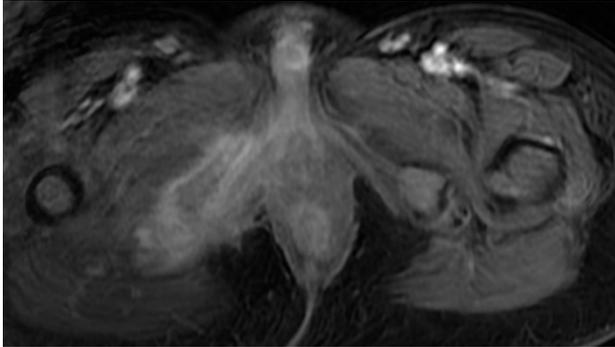

Figure 2. Axial T1 postcontrast MRI of the pelvis showing decreased T1 signal within the right ischium with peripheral enhancement

On admission, her laboratory data were remarkable for anemia with a hemoglobin of 6.8g/dL, hyponatremia, hypomagnesemia, renal function was normal, urinalysis was positive for large leukocyte esterase, nitrates, white blood cells, red blood cells, protein and SSA +4. T cell CD4$^+$ 4, viral load 58000, flow cytometry showed CD3 absolute count 460, CD3/CD4 Absolute 6, CD19 absolute count 29.

Patient received packed red blood cells transfusion and magnesium replacement. She was started on Ceftriaxone for 1 gram daily. Hyponatremia managed with fluid restriction. Nystatin and fluconazole were given to manage her oral and esophageal candidiasis. Tylenol and opioids were provided for pain control.

Since the patient insisted for a radical surgery "to remove completely the fungating mass"; GYN-Oncology service knew the patient well from previous outpatient encounters and deemed the patient not a surgical candidate.

Figure 3. Coronal CT cystogram of the abdomen and pelvis showing osseous destruction of the bilateral pubic rami (red arrow). Uterus fibroid calcification (yellow arrow)

An abdominal/pelvic computed tomography Scan (CTS) demonstrated enlarged multilobulated uterus with a fibroid calcification measuring 9.5x10.3x8.3 cm. Direct invasion

of the right and left inferior pubic rami, with pathologic fracture of the right inferior pubic rami and osseous destruction of the bilateral pubic rami appreciated on Axial, sagittal and coronal CTS Abdomen/Pelvic views (Figure 3 - Figure 5).
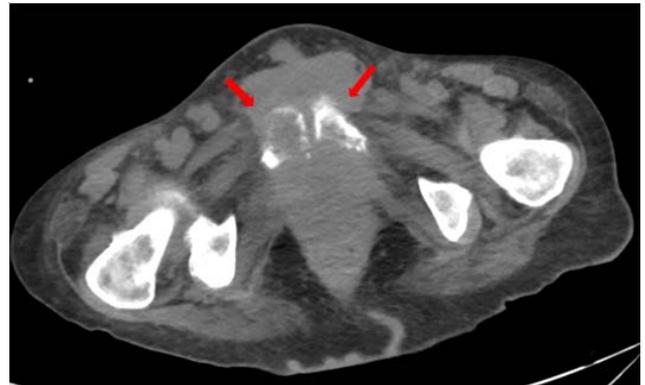

Figure 4. Axial non-contrast CT of the pelvis showing an anterior pelvic mass causing erosion of the bilateral pubic rami (red arrow)

Figure 5. Sagittal post-contrast CT cystogram of the abdomen and pelvis showing a pelvic mass with osseous destruction of the pubic rami

The hospital course was complicated by the following: acute kidney injury, urinary bladder outlet obstruction requiring suprapubic catheter placement by the Urology service and pneumoperitoneum.

After the patient had returned from the urological procedure to place the suprapubic catheter, she became tachycardic and pulmonary embolism was suspected. A ventilation perfusion scan was obtained given the ongoing acute kidney injury which was negative for venous thromboembolism. However, a chest imaging revealed pneumoperitoneum (Figure 6) along the anterior surface of the liver, within the mesenteric planes between the antrum/duodenum and liver surface. A non-contrast abdominal computed tomography revealed also small scattered foci of pneumoperitoneum, small amount of fluid in the anterior pelvis, and enlarged calcified fibroid uterus, with 1 cm lingular nodules concerning for metastasis. The patient underwent exploratory laparotomy and a revision of the suprapubic catheter. The patient tolerated the procedure without complications.

Table 1. Patient's selected laboratory results

Laboratory data	On admission	HD # 7	HD # 9	HD # 11	HD # 12	HD # 16
White blood cells (K/ul)	8.44	9.92	10.65	13.29	7.91	8.34
Red blood cells (M/ul)	2.72	3.11	3.23	3.72	2.90	3.42
Hemoglobin (g/dl)	6.8	8.3	8.3	9.2	7.2	9.8
Hematocrit (%)	22.6	25.7	26.5	32.7	24.6	29.5
Mean corpuscular volume (fl)	83	82.8	81.9	87.9	84.7	86.3
Blood Urea Nitrogen (mg/dl)	23	21	23	42	21	4
Creatinine (mg/dl)	1.04	0.87	2.47	3.52	0.77	0.37
Sodium (mmol/L)	128	134	130	134	135	134
Potassium (mmol/L)	3.6	3.8	4.4	5.2	4.4	3.5
Bicarbonate (mmol/L)	24	23	17	14	16	23
Albumin (g/dL)	2.97	2.84	NA	NA	2.27	1.81

Figure 6. Portable chest x-ray demonstrating pneumoperitoneum, visible as a crescentic lucency under the right hemidiaphragm (red arrow)

The patient's symptoms improved, four days post-operatively AKI resolved with IV fluid management and supportive care. The patient was discharged to a rehabilitation center with outpatient follow-ups for HIV, Urology and Oncology clinics. Goals of care were also addressed with the patient however, she opted for leaving the discussion for future encounters.

2. The Clinical Problem

Vulvar cancer is a rare type of cancer affecting only women, comprising approximately 5% of all gynecological cancers. [1] Vulvar cancer has an estimated incidence of 5,000 cases per year in the United Sates, resulting in 1,000 deaths per year. [2] Almost 90% of vulvar cancer is squamous cell carcinoma (SCC). [1] Vulvar SCC arises from two types of vulvar intraepithelial neoplasia (VIN): usual and differentiated. [3] VIN of the usual type is HPV-driven and has either a warty or basaloid histology. [4,5] HPV primarily affects younger women and is the precursor lesion in nearly 40% of all cases of vulvar SCC. [1,6] Vulvar SCC that develops without underlying HPV infection has a keratinizing histology and often demonstrates p53 inactivation. [4,5]

3. Key Clinical Points

Sexually transmitted Human papilloma virus (HPV) related cervical cancer, was the fourth most common cancer among women in the world in 2018 [7], on the other hand, Vulvar squamous cell carcinoma (VSCC) is a rare tumor of the female genital tract, and accountable for 5% of all the genital tract malignancie [8].

Basic method for cervical cancer screening is Pap smear which combined with HPV test in most of the times [9]. Mario Preti, et al. study on VSCC cases identified HPV as the causative object for vulvar carcinogenesis [10], as currently there are no recommended screening strategies for vulvar cancer, HPV immunization through vaccination may be the only effective way for prevention [11].

The most common initial symptom of vulvar cancer is pruritus, which may be of a long duration. Vulvar pain, discharge, and bleeding are less commonly reported. Although vague symptoms contribute to the delayed initial presentation of the disease, studies have shown greater delays in patients affected by noninflammatory disorders of vulva including atrophy, hypertrophy, and cyst than those with diseases of Bartholin's gland with a mean delay of 186-328 days [12].

Most of the vulvar cancers are diagnosed at the stage of localized tumors and as low as 2.8% of vulvar cancer had distant metastases at the time of diagnosis [13].

Vulvar carcinoma usually has a lymphogenic dissemination with inguinofemoral lymph nodes being the primary site [14]. Hematogenous distant metastasis such as lung, liver, and bone, usually occur late in the disease course. In rare instances, cutaneous metastases can be seen in vulvar carcinoma, with short survival being a predominant feature [15]. In this case admission happened at an advance stage with already involved inguinofemoral lymph nodes and pelvic bone due to poor follow-up.

4. Strategies and Evidence

4.1. Diagnosis and Evaluation

Vulvar SCC tends to have delayed diagnosis. Rhodes et al. showed more than one-year delay in vulvar SCC diagnosis even in symptomatic patients [16].

There are two systems used for this malignancy staging: The Tumor, Node, Metastasis (TNM) system and International Federation of Gynecology and Obstetrics (FIGO) staging systems [17] which are explained below:

TNM staging system: [16]
1. T-Primary Tumor:
    1.1. Tx- Primary tumor cannot be assessed

1.2. T0- No primary tumor

1.3. Tis- Carcinoma in situ

1.4. T1- Tumor confined to vulva or vulva and perineum

 1.4.1 T1a- Tumor dimension≤2cm or with stromal invasion≤ 1mm

 1.4.2 T1b- Tumor dimension>2cm or with stromal invasion >1mm

1.5. T2- Tumor of any size with extension to lower third of urethra, lower third vagina and anus

1.6. T3 (T4 FIGO)- Tumor of any size with extension to upper two-third of urethra, upper two-third of vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone tumor

2. N: Regional lymph nodes:

 2.1. Nx- Regional

 2.2. N0- Cannot assess any regional nodes

 2.3. N1- Metastases to lymph nodes as below:

  2.3.1 N1a- 1 or 2 metastatic lymph nodes, with size of <5mm each one

  2.3.2 N1b- l metastatic lymph node≥5mm

 2.4. N2- Metastatic lymph nodes as below:

  2.4.1. N2a- 3 or more metastatic lymph nodes, each<5mm

  2.4.2. N2b- 2 or more metastatic lymph nodes, each≥5mm

  2.4.3. N2c-Metastatic lymph nodes with extracapsular spread

 2.5. N3- Fixed or ulcerated regional lymph node metastasis

3. M: Distant metastasis

 3.1 M0- None

 3.2 M1- Distant metastasis [16]

 FIGO staging system: [17,18]

Stage I- Tumor confined to the vulva

- IA- Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm[a], no nodal metastasis.
- IB- Lesions > 2 cm in size or with stromal invasion > 1.0 mm[a], confined to the vulva or perineum, with negative nodes.

Stage II- Tumor of any size with extension to adjacent perineal structures (⅓ lower urethra ⅓ lower vagina, anus) with negative nodes.

Stage III- Tumor of any size with or without extension to adjacent perineal structures (⅓ lower urethra ⅓ lower vagina, anus) with positive inguinofemoral lymph nodes.

- IIIA- With 1 lymph node metastasis (≥ 5 mm) or, 1–2 lymph node metastasis (es) (< 5 mm)
- IIIB- With 2 of more lymph node metastases (≥ 5 mm), or 3 or more lymph node metastases (< 5 mm)
- IIIC- With positive nodes with extracapsular spread

Stage IV- Tumor invades other regional (⅔ upper urethra, ⅔ upper vagina) or distant structures.

- IVA- Tumor invades any of the following: Upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone or fixed or ulcerated inguinofemoral lymph nodes.
- IVB- Any distant metastasis including pelvic lymph nodes [18].

4.2. Management

Noninvasive methods are used to evaluate the disease extension prior to the operation [18]. In some cases, magnetic resonance imaging is useful to evaluate the tumor extension and lymph node involvement [18]. Surgery is associated with increased mortality rate [18]. Currently radical local excision with inguinofemoral lymph node resection is the standard method of management in vulvar cancer [19].

Although limited study found radiation therapy alone or with lymph node dissection combination as an effective treatment, but inguinal lymph node number and diameter, and required therapeutic irradiation dose are in uncertainty [20].

Therapeutic management for vulvar SCC with metastasis is preferred to be chemotherapeutic palliative regiment and usually are the same regimen which chosen for advanced cervical or anal cancers [19]. To date, there is no specific chemotherapeutic regimen for both type of vulvar SCC, HPV-related or HPV-independent tumors [15].

4.3. Areas of Uncertainty

Vulvar SCC can progress rapidly, become refractory to chemotherapy and can unexpectedly show dismal prognosis even if diagnosed at an early stage [15]. There is an urgent need for novel treatment, work-up, screening and diagnostic guideline. Psychotherapy should be employed early on as well to improve patient compliance and emotional wellbeing.

4.4. Complication

Patients with vulvar SCC are subject to many catastrophic complications that can be mainly divided into physiological and psychological. As the tumor grows it invades the surrounding areas causing pain, discomfort and deformity. Just like our patient, mass effect may cause damage to surrounding urogenital and reproductive organs. Invasion of surrounding nerves and vasculature can aggravate pain and cause hyper viscosity syndromes. Pelvic bones are destroyed and may need to be surgically removed with the tumor. On top of this, patients are at risk of complex surgical procedures and prolonged hospitalizations. Although our patient's tumor was unsalvageable via surgery, she developed obstructive uropathy leading to acute kidney injury. An attempt at suprapubic catheter targeted at an area already disfigured by tumor and caused pneumoperitoneum, leading to reversal of the catheter. Our case shows the various deteriorating complications caused by vulvar SCC when permitted to grow to advanced stages.

Gynecological lesions can affect a patient's quality of life, sexual activity, emotional wellbeing which is even more enhanced with malignancy and its invasive treatments. Therefore, psychotherapy is equally important in cancer management. Studies have shown improvement if quality of life, emotional and social functioning in patients with psychotherapy. Our patient was not contacted with a psychiatrist, but it is possible that such an intervention at an earlier stage may have improved her compliance and consequently the outcome of her disease [21].

5. Conclusions and Recommendations

Cancer of the vulva consists of 3 to 5% of all gynecologic malignancies. The most common initial symptom of vulvar cancer is pruritus, which may be of a long duration. Vulvar pain, discharge, and bleeding are

less commonly reported. These findings underscore the need for patient and physician education regarding the early diagnosis of carcinoma of the vulva and the importance of having a biopsy diagnosis before treating vulvar lesions. A biopsy of the vulva is a simple procedure that can be performed in the outpatient setting; in our patient, there was a delay in diagnosis and in treatment due to the patient's lack of non-compliance. A careful inspection of the vulva should be a part of every gynecologic examination and any lesion should raise the suspicion of malignancy in the differential diagnosis for vulvar lesions in young women. We must consider biopsies for all suspicious vulvar lesions, even in young and pregnant women. Early and thorough diagnosis with subsequent appropriate definitive treatment is the principle of the increase the survival change.

In general, there is wide access to HPV immunization through vaccination [22], and the fact that currently there are no recommended screening strategies for vulvar cancer, HPV vaccination may be the only effective way for prevention of this malignancy [23]. Our patient was not aware of her HPV vaccination status which serves as a lesson emphasizing the importance of patient education about the importance and impact of HPV immunization.

Patients 11-12 years old and up to 26 years of age should be administered HPV vaccine. The benefit is higher to the female group however, both genders should receive the vaccine and immunization should happen before sexual activity starts. Since HPV types 16 and 18 are associated with about three quarter of the malignancies (oropharyngeal, cervical, anal, vulvar cervical and penile) these serotypes are included in all of the HPV vaccine available for use [24,25].

Among the various factors contributing to delayed initial presentation include cultural and religious stigmata as well as low socioeconomical status. The study of Fokom Domgue et al. carried out on US population showed severe knowledge gaps and inaccurate beliefs about the importance and preventive benefit of the HPV vaccination among US women [26].

Similar results were found in Moroccan women by Fatima et al. in 2016 [27]. Our patient belonging to an unprivileged community likely lacked education and understanding of the gravity of the situation upon being diagnosed with high grade SCC on biopsy initially and declined treatment. Once her disease advanced causing debilitating symptoms, she wanted surgical removal of the tumor, but it was deemed non operable at that stage. By the time our patient presented to our facility, her SCC had locally advanced with involvement of inguinofemoral lymph nodes and pelvic bone.

Therefore, future interventions aiming to increase population-level knowledge about the benefits of the HPV vaccine is required, which along increased healthcare providers' efforts in patient education about HPV vaccination and subsequent lifesaving benefits are likely to impact patient outcomes.

Acknowledgements

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