Acute Marjolin’s ulcers following Genital Ulcer Disease in an HIV-infected Adult Nigeria

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Abstract

Marjolin’s ulcer is an aggressive malignancy that may complicate chronic neglected ulcers. Acute Marjolin’s ulcer is a very rare form of this disease which has not been previously reported in HIV/AIDS patients with genital ulcer disease (GUD). A 28 year old HIV-1-infected Nigerian female presented with a three month history of chronic genital ulcers associated with fistula and sinuses, as well as bilateral inguinal lymphadenopathies and right leg lymphedema. After about two months of follow up, the genital ulcers evolved into a fungating proliferative ulcer. A biopsy of the ulcer revealed a well differentiated invasive squamous cell carcinoma-a typical feature of Marjolin’s ulcer.

This case is reported to alert clinicians on the need for prompt recognition and treatment of all cases of GUDs in HIV/AIDS patient, in order to mitigate the potential of malignant transformation of HIV-related chronic genital ulcers to Marjolin’s ulcers.

Introduction

Marjolin’s ulcers are rare highly aggressive skin malignancies that result from previously traumatized, chronically inflamed or scarred skin. These ulcers were first described in 1828 by a French surgeon, named Jean Nicolas Marjolin, but it was DaCosta who first coined the expression “Marjolin’s ulcer” in 1923 to describe malignant tumors forming over burn injuries. Although majority of Marjolin’s ulcers follow neglected burn injuries, there have been reports of these ulcers following chronic inflammation resulting from traumatic injuries, penile human bite scar, pressure sores, chronic non-healing ulcers, and chronic osteomyelitis. Diabetic foot ulcer, Fournier’s gangrene, urinary fistulas, and venous insufficiency ulcers, as well as chronic lymphedema, and chronic ulcers of leprosy are other known forerunners of Marjolin’s ulcers.

Two types of Marjolin’s ulcers have been described in the literature, including the acute and chronic forms. Acute Marjolin’s ulcer is a quite rare form of the disease with a short latent period of less than 1 year while the chronic form has a latent period of greater than 1 year. The latent period for chronic Marjolin’s ulcers ranges from 16 years to 30 years, with shorter latency reported in Sub-Saharan Africa.

Acute Marjolin’s ulcer was first described among elderly patients following burn’s injuries, and the rapid progression to malignancy may be attributed to reduced ability of the skin of the elderly to withstand trauma and carcinogenic insults. The development of acute Marjolin ulcers may not solely be attributable to burn injuries as it has also been described in a 65 year female following tooth extraction.

Genital ulcer diseases (GUD) due to sexually transmitted infections (STI) are most common causes of chronic genital ulceration in HIV/AIDS patients. While most cases of GUD in the general healthy population are acute, uncomplicated and easily treatable, GUD in HIV/AIDS patient has been shown to be atypical, chronic, complicated and difficult to treat.

Malignant squamous cell transformation of Donovonosis, a GUD caused by Klebsiella granulomatis, has been reported in an HIV-negative adult male from India. There is paucity of reports of any form of Marjolin’s ulcers resulting from GUD in HIV/AIDS patients, especially from Nigeria. Consequently, I hereby report a case of acute Marjolin’s ulcer following a chronic genital ulcer disease in an HIV-infected adult female who was referred to Bingham University Teaching Hospital, Jos Plateau State. This case highlights the complexities of definitive treatment.
diagnosis of GUD in HIV-infected patients in resource limited settings as well as the various challenges associated with managing GUDs in HIV-infected patients. It is also hoped that this case report will improve awareness among clinicians about the need for early diagnostic work-up and treatment of all GUD in HIV/AIDS patients.

Case report

A 28-year-old single unemployed female university graduate was referred to our facility with a 3-month history of left painful nodular inguinal swelling, associated with a left-sided painful vulva ulcer. She then observed progressive nodular inguinal swellings in both inguinal regions with increase in size of vulva ulcers associated with malodorous purulent discharge. These symptoms were accompanied by progressive painless swellings of the whole of the left lower limb. Before referral, the left inguinal swellings had repeatedly been incised and drained in an attempt to relieve the left leg swelling. She had also received multiple antibiotics for variable periods including injection ceftriazone, and oral ofloxacin, amoxicillin/clavulante (augumentin), ampiclox and metronidazole, among others. She had also received anti-tuberculosis drugs (RHZE) for over 2 months prescribed at a peripheral clinic on account of a suspicion of tuberculosis lymphadenopathy. Although, she had observed some weight loss since onset of her symptoms, there was no accompanying history of cough, fever or night sweats. She was diagnosed with HIV-1 infection about one year prior to presentation and had commenced first line antiretroviral drugs (Zidovudine, Lamivudine, and Nevirapine) on account of a low CD4 cell count of 264 cells/μl. She however defaulted on ART after two months of initiation of therapy for undisclosed reasons. She gave a history of multiple sexual partners and a past history of termination of pregnancies. On examination, she was depressed, wasted, afebrile, and mildly pale. There was no significant peripheral lymphadenopathy, no oral thrush and no extra-genital ulcers. The whole left lower limb was oedematous, non-pitting and non-tender, suggestive of lymphedema [Figure 1]. Examinations of the

Chest, Cardiovascular, and Gastrointestinal systems were essentially normal. Examination of the external genitalia and groin revealed a linear post surgical incision hypertropic scar over the mid-portion of the groin with nodular swellings of the inguinal and femoral lymph nodes of the right groin giving the appearance of a ‘groove sign’ [Figure 1]. There were fistula and sinuses along the left inguinal region discharging scanty mucopurulent fluid, as well as multiple left vulvovagina ulcers which were soft and tender, with an undermined and irregular edge and a base covered with mucopurulent exudates [Figure 2]. The whole vulva and the left groin were oedematous.

Figure 1: Groin and inguinal region of HIV-infected female with genital ulcer disease. There is evidence of lymphedema of the right leg and enlargement of the right inguinal and femoral lymph nodes giving the appearance of a ‘groove sign’.

Figure 2: Irregular vulvovagina ulcers with an undermined and irregular edges, and mucopurulent exudative base. There are fistula and sinuses along the left inguinal region.
Based on the symptoms and pattern of ulceration, a clinical diagnosis of Chancroid complicated by lymphedema was made. Lymphogranuloma venerum and Granuloma inguinale were considered as differential diagnoses. An initial cytology of the discharge from the left inguinal nodular swellings revealed non-specific chronic inflammation. Routine culture of the discharge yielded no growth. Culture for tuberculosis and atypical organisms such as Chlamydia and Hameophilus ducreyi could not be done due to resource constraints. There were also no facilities for pathogen-related nucleic acid amplification testing. Histology of the excised left inguinal lymph nodes was also suggestive of non-specific chronic inflammation without evidence of granuloma or lymph node tuberculosis. Mantoux was non-reactive and Chest X-ray was normal. Her packed cell volume was 27% and total white cell count of 2.8 x 10^3/L, consisting of 78% neutrophils and 20% lymphocytes. Her CD4 had dropped from 264 cells/ul to 165 cells/ul. The renal function test results were essentially normal and Veneral Disease Research Laboratory screening for syphilis was negative. In view of lack of confirmatory laboratory diagnosis, a final syndromic diagnosis of genital ulcer disease with inguinal bubo was made. She received therapy for syndromic management of inguinal bubo including ciprofloxacin 500mg twice daily and doxycycline 200mg daily for 6 weeks. Intravenous dexamethasone 8mg 8hourly was given for 48hours to reduce oedema. Antiretroviral therapy (Tenofovir, Lamivudine and Nevirapine) and prophylactic oral septrin 960mg daily were recommenced after adherence counselling. Debridement of the ulcers was undertaken by the surgical unit and she was subsequently referred to a government hospital close to her home for daily dressing of the ulcers. Despite being regular on medications and after two months of follow up she presented with a fungating ulcer-proliferative mass protruding from the vulva and involving the whole of the left groin and the whole of the left groin [Figure 3]. A biopsy of this mass was suggestive of well differentiated invasive squamous cell carcinoma consistent with Marjolin’s ulcer. She was referred for definitive therapy in a surgical oncology centre but was lost to follow up.

**Figure 3:** Fungating ulcer-proliferative mass protruding from the vulva and involving the whole of the left groin— a case of acute Marjolin’s ulcer following genital ulcer disease

**Discussion**

The lists of differential diagnosis of genital ulcers with or without associated inguinal lymphadenopathy may include Chancroid, LGV, Granuloma Inguinale, Herpes Simplex ulcers, and Syphilis. Although there have been case reports of genital ulcers due to tuberculosis, tuberculosis-related genital ulcers are rare. Non-sexually transmitted diseases such as Behcets syndrome, pemphigus, Crohn’s disease, erosive lichen planus and fixed drug eruptions may also cause genital ulcers. The multiplicities of differential diagnosis may account for the variety of medications received by the patient before referral to our facility. The confirmatory diagnosis of specific GUDs in HIV-infected patients is often fraught with difficulties due to a variety of reasons. First, the clinical presentation of GUDs is often atypical with overlapping similarities in the symptomology and clinical signs independent of the type of GUD. The initial clinical diagnosis of Chancroid in our patient was based on the clinical presentation of a soft, irregular painful ulcer associated with inguinal lymphadenopathy as described in the literature. However, this patient also presented with features of groove sign which according to the literature is almost pathognomic of LGV. Furthermore, the presence of bilateral lymphadenopathy, lymphedema and multiple fistulae are more
supportive of LGV than Chancroid.\textsuperscript{12,22} Our case illustrates the lack of specificity and sensitivity in clinical diagnosis of GUDs as have been suggested by many other studies.\textsuperscript{23,24} Secondly, clinical diagnosis might be inaccurate due to mixed infections, as have been reported in HIV-infected patients.\textsuperscript{23} In view of the present features of both Chancroid and LGV in our patient, mixed infections remain a possibility.

The third difficulty in the diagnosis of GUDs is the lack of sensitivity in confirmatory laboratory diagnosis even in centres with facilities to culture atypical organisms such as Chlamydia and Haemophilus ducreyi and to detect pathogen nucleic acid through techniques such as polymerase chain reaction.\textsuperscript{17,20,23} Unfortunately, most tertiary hospitals in Nigeria do not even have the required facilities or resources to confirm GUDs in the laboratory as illustrated in our case.

In view of these complexities in the diagnosis of GUDs and in order to promptly treat all cases of GUD, the World Health Organisation has recommended a syndromic approach to the management of GUDs.\textsuperscript{25} This approach has been validated as practicable, reliable and cost effective in the prevention and management of GUDs even in the developed world.\textsuperscript{26,27} Consequently, our patient was managed using the syndromic diagnosis of inguinal bubo.

Prompt therapy of uncomplicated GUDs, even in HIV-infected patients, is associated with complete recovery.\textsuperscript{25} However, our patient presented after 3 months of symptoms and at a time when unnecessary and inappropriate incision and drainage of inguinal buboes had been done leading to multiple chronic non-healing ulcers. In the management of inguinal buboes, it is recommended that nodes should be aspirated only through normal skin for healing to be guaranteed.\textsuperscript{17,25} Chronic ulcers, irrespective of their site of origin, are known risk factors for Marjolin’s ulcers.\textsuperscript{1,2} Although, Marjolin’s ulcers have been reported in Nigeria, mainly following burns,\textsuperscript{5,6} this case is perhaps the first case report of acute Marjolin’s ulcers in an HIV/AIDS patients following GUD in Nigeria. Squamous cell carcinoma is the commonest histological variety seen in Marjolin’s ulcers but other histological varieties like basal cell carcinomas, malignant melanomas, fibrosarcomas, liposarcomas, have also been reported.\textsuperscript{2} Occasionally, more than one histologic variant may be seen within the same scar.\textsuperscript{2} The aetiology of Marjolin’s ulcers is thought to be multi-factorial but similar for all histological variants of the disease.\textsuperscript{2}

The mechanisms of transformation of chronic ulcers to Majorlin’s ulcers have been linked to cellular instability due to chronic irritation, toxins release from damaged tissues, poor lymphatic flow due to obstruction and decreased vascularity of scar tissue leading to impaired immune surveillance.\textsuperscript{2,8} Other proposed mechanisms include immunosuppression due to decrease T cell counts and genetic mutations of tumour suppressor gene p53 and Fas gene.\textsuperscript{2,8} Environmental and genetic triggers are thought to predict shorter latent period in patients with acute Marjolin’s ulcers.\textsuperscript{2} It is therefore plausible that HIV/AIDS-related immunosuppression played a key role in the rapid transformation of the GUD in our patient to acute Marjolin’s ulcer.

Complete surgical excision of tumour and subsequent skin grafting remains the mainstay of treatment of Marjolin’s ulcers.\textsuperscript{1,2} The ulcers however respond poorly to radiotherapy and chemotherapy due to relative poor vascularity and extensive fibrosis. Marjolin’s ulcers generally have a poor prognosis, with propensity to metastasize to adjoining lymph nodes. Prognosis is worse with shorter latent periods, tumour size greater than 2cm, and with well differentiated tumours. Prompt and adequate management of all ulcers and injuries as well as early excision of unstable scar tissues associated with chronic ulcers and burns remain most effective means of preventing the development of Marjolin’s ulcers.\textsuperscript{1,2}

**Conclusion**

Marjolin’s ulcer, an aggressive malignancy of chronically irritated skin, may accompany chronic GUD in HIV/AIDS patients, especially in patients with significant immunosuppression as illustrated in our case.
report. To avert these and other complications associated with GUD in HIV/AIDS patients, clinicians ought to be vigilant to detect and treat GUD in HIV/AIDS patient in a timely and syndromic fashion.

REFERENCES


