Acral and Multicentric Pigmented Bowen’s Disease in HIV-Positive Patients: Report on Two Unusual Cases

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Abstract
In situ squamous cell carcinoma of the skin (SCCis or Bowen’s disease) is a common intraepidermal cutaneous malignancy with a low invasive potential. Acral Bowen’s disease is usually solitary, but multiple acral SCCis have been reported. Pigmented Bowen’s disease is typically unilesional and characterized by a hyperpigmented plaque with a velvety of keratotic surface, which can eventually simulate melanoma clinically. We describe two HIV-positive patients who presented with multiple pigmented SCCis involving the distal extremities. In patients with immunosuppression, the presence of multiple and hyperpigmented verrucae that clinically do not respond to adequate treatment should raise the differential diagnosis of SCC in situ.

Key Words: Acral, Bowen’s disease, HIV, pigmented

Introduction
In situ squamous cell carcinoma of the skin (SCCis or Bowen’s disease) is a common intraepidermal cutaneous malignancy with a low invasive potential (3%). It usually presents as a single erythematous scaly macule or plaque on sun-exposed skin and uncommonly as multiple lesions (10%–20%). Less frequently (1.7%), SCCis can display pronounced clinical pigmentation, and only scarce reports exist on multiple pigmented SCCis. Acral SCCis usually involves a sole digit, but scarce number of cases on multiple acral SCCis have been described. We describe two HIV-positive patients who presented with multiple pigmented SCCis involving the distal extremities.

Case Reports
Case 1
A 25-year-old male diagnosed with HIV 7 years ago, who begun antiretroviral therapy (ART) with emtricitabine/tenofovir/ritonavir/atazanavir, only 2 months before his visit to the dermatology clinic, presented with long-standing perianal condyloma acuminata and an 8-month history of a steadily enlarging tumor involving the nail bed of the ring finger of his right hand. The tumor occupied the entire nail bed, distal matrix, and peripheral nail folds, thus producing anonychia; it had irregular borders and a keratotic hyperpigmented surface with focal areas of red discoloration. The extension of the brown pigment to periungual skin folds additionally created a pseudo-Hutchinson’s sign (Figure 1). Dermoscopy of the tumor showed a scaly, hyperkeratotic, and pigmented tumor with underlying small dotted and comma vessels and a regression-like area, although the absence of pigment network was observed. With a clinical suspicion of subungual acral melanoma, a longitudinal biopsy of the nail apparatus was performed revealing a highly atypical keratinocytic proliferation...
involving the full thickness of the subungual epithelium and extending from the hyponychium to most of the proximal nail matrix. Neoplastic keratinocytes were highly pigmented and scattered monomorphous highly pigmented dendritic melanocytes were appreciated in the basal layer of the neoplasm (pigmented subungual SCCis). At the time, the patient had a total CD4+ T-cell count of 8 cells/µL (10% of all circulating T-cells) and a viral load of 14,636 copies/µL (log 4.17). The patient underwent complete resection of the nail apparatus including a 5 mm margin of uninvolved skin with immediate reconstruction through a full-thickness skin graft. Four months later, the skin graft had successfully healed, but two new similar lesions on the periungual area of the thumb and little finger of the left hand were present. At this time, the patient already had an undetectable viral load with 76 CD4+ cells/µL. Biopsies of such new lesions showed pigmented SCCis and complete excisions followed. A couple of months after both surgeries, viral load was undetectable with 127 CD4+ cells/µL. There was no recurrence of the lesions during a 3-year follow-up.

**Case 2**

A 38-year-old male with a 6-month HIV diagnosis under ART (efavirenz/emtricitabine/tenofovir) presented to the dermatology department with a 1-year history of multiple (more than 6) hyperpigmented and velvety plaques localized to both hands and feet, affecting interphalangeal and periungual skin [Figures 2a and b]. Dermoscopy showed the presence of reticular pigment and areas with multiple dotted vessels [Figure 2c]. A former diagnosis of warts had been given, and the patient received topical keratolytics without objective improvement. At that time, he had an undetectable viral load with 56 CD4+ cells/µL. Biopsies from four different skin lesions were performed which showed clear signs of pigmented SCCis. A conservative approach was selected and topical 5-fluorouracil cream was prescribed, leading to a slow regression of the lesions, with a total resolution of all of them in almost 18 months. At that time there were undetectable viral load and 364 CD4+ cells/µL. Three-year follow-up did not show recurrence of the lesions.

**Discussion**

Acral Bowen's disease is usually solitary, but multiple acral SCCis have been reported.[5] Likewise, pigmented Bowen's disease is typically unilesional and characterized by a hyperpigmented plaque with a velvety or keratotic surface, which can eventually simulate melanoma clinically.[6-8] Pigmented Bowen's disease is described more frequently in dark-skinned individuals with a propensity to involve sun-shielded areas; when acral skin is involved, men and older patients are more commonly affected.

Nail dystrophies secondary to acral SCC or SCCis can be easily misdiagnosed and a pseudo-Hutchinson’s sign, although rare, can be present. The differential diagnosis of acral SCCis is broad and depending on its exact location and the presence or absence of pigmentation includes chronic paronychia, onychomycosis, verruca vulgaris, fibrokeratoma, traumatic nail dystrophy, melanocytic nevus, superficial spreading melanoma, and outside of the nail apparatus also pigmented actinic keratosis, seborrheic keratosis, and basal cell carcinoma.
Bowen’s disease of the nail bed and periungual area may additionally mimic various inflammatory and infectious conditions.

Histopathological examinations of pigmented SCCis show classic changes of conventional SCCis in association to hyperpigmentation of basal keratinocytes. In some cases, highly melanized dendritic melanocytes are seen intermingled with basal layer keratinocytes as observed in one of our patients.\(^{[9]}\) The exact reason for the pigmentation in SCCis still remains elusive; however, the induction of melanin synthesis by neoplastic keratinocyte-derived cytokines has been hypothesized.\(^{[10]}\) Another alternative, in cases truly induced by human papillomavirus (HPV), would be that the viral subtype played a role in the induction of pigmentation as described for pigmented warts in certain ethnic groups.

Both of our patients were infected with HIV, a condition known to predispose to HPV infection, which in turn was commonly associated with the development of SCC, particularly among immunosuppressed individuals. It was, however, challenging to conclusively implicate HPV as the causative factor for Bowen’s disease since the presence of HPV DNA was found only in 30%–58% of extragenital SCCis and we had no institutional means of objectively testing for HPV in the tumors. However, it would be reasonable to assume a role of HPV in our cases.

Various therapeutic options have been described for SCCis, including topical treatments, superficial destructive techniques, CO\(_2\) laser and surgical excision. In one of our patients, surgical excision with oncological margins was deemed preferable due to the rapid evolution of the neoplasm to involve nearly the entire nail apparatus. In our second patient, the slow progression of his numerous tumors made it reasonable to opt for a less aggressive approach with 5-fluorouracil cream BID, with complete resolution of all lesions after almost 18 months of treatment.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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