p16$^+$ Squamous cell carcinoma in situ masquerading as genital psoriasis

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INTRODUCTION

Cutaneous neoplasms of the male genitalia are an important consideration in older men and immunocompromised patients. They are derived from the squamous epithelium and have an association with human papilloma virus (HPV).[1] HPV types 16, 18, and 57b have been isolated, and their DNA is present in approximately 40% to 45% of all penile carcinomas.[2,3] Squamous cell neoplasia includes both squamous cell carcinoma in situ (SCCIS) and invasive carcinoma. Risk factors include increasing age, immunosuppression, smoking, exposure to ultraviolet light, benzene, and arsenic. Invasive squamous cell carcinoma is uncommon in the genital region.[2] It may advance from SCCIS or present as a more aggressive tumor. In general, both invasive squamous cell carcinoma and SCCIS can present as erythematous patches or plaques with or without significant scale on the penis and inguinal skin.

Many conditions mimic SCCIS in the inguinogenital region. Intertrigo, psoriasis, dermatophytosis, candidiasis, Darier disease, Hailey-Hailey, plaque stage cutaneous T-cell lymphoma, and extramammary Paget disease can all resemble SCCIS. Genital psoriasis, in particular, is underrecognized. Involvement of the genital area occurs in 29% to 46% of all psoriasis patients. The symptoms of genital psoriasis are mild to moderate, with itch, pain, and burning most commonly reported. These symptoms closely mimic those of SCCIS. Scale is often absent in genital psoriasis.[4]

Here we report a case of SCCIS that closely resembled genital and inverse psoriasis. The tumor was found to be strongly p16$^+$ for an HPV marker in this patient who was later found to be immunosuppressed. The treatment of genital SCCIS is reviewed here with attention to factors that can influence choice of therapy.

Abbreviations used:

HPV:	human papilloma virus
MGUS:	monoclonal gammopathy of undetermined significance
PIN:	penile intraepithelial neoplasia
SCCIS:	squamous cell carcinoma in situ

CASE REPORT

An otherwise healthy 51-year-old man noted intensely pruritic lesions on the penis, scrotum, pubis, and gluteal region for 3 years. There was no prior history of psoriasis, eczema, or genital warts. History included a basal cell carcinoma on the bridge of the nose that was treated with Mohs micrographic surgery, facial herpes simplex, seborrheic dermatitis, and idiopathic erythema nodosum. He had no prior exposure to arsenic and was HIV negative.

Examination found sharply demarcated salmon-red plaques with mild scale on the genitocrural and gluteal skin (Fig 1). The features were considered typical of inverse psoriasis, and he was treated with acitretin, 10 mg/d, together with betamethasone valerate 0.1% cream.

When there was no improvement with treatment, the gluteal plaque was biopsied. Biopsy

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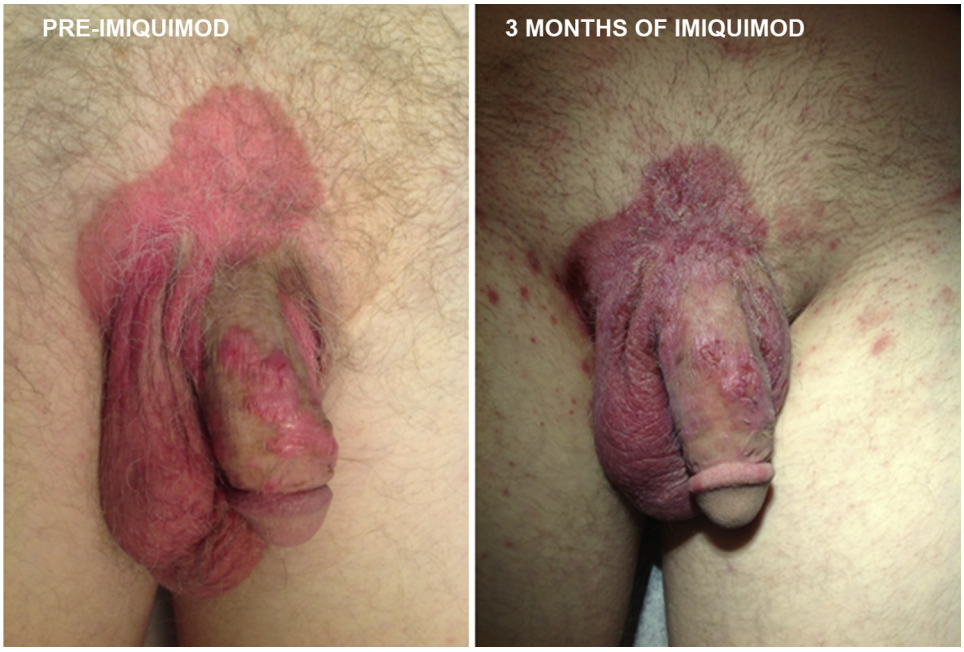

Fig 1. Clinical presentation and response to treatment with imiquimod.

results showed epidermal acanthosis and hyperkeratosis, with some mild atypia and possible viral cytopathic effect: the changes were suggestive of a viral wart. Repeat biopsies of the penis, scrotum, and pubis all found full-thickness epidermal dysplasia typical of SCCIS, with immunohistochemical staining for p16 being strongly positive within the tumor (Fig 2).

The patient received a diagnosis of unusually extensive multifocal genital and perineal SCCIS. Further workup for immunodeficiency and paraproteinemia was performed in light of a normal complete blood count and negative HIV result. Testing of immunoglobulin levels and a serum protein electrophoresis uncovered IgA monoclonal gammopathy of undetermined significance (MGUS). No evidence of multiple myeloma was found. Proctoscopy and colonoscopy were normal.

The patient was treated with imiquimod cream 5% five times per week. Little improvement occurred after 3 months of therapy (Fig 1). A longer course, even with application site rotation, could not be tolerated because of crusting and discomfort. He recently switched to using 5% 5-fluorouracil cream but had only moderate improvement with twice-daily therapy for 8 weeks. Radiotherapy was declined because of potential complications. Cost prohibited attempting carbon dioxide laser or photodynamic therapy. Capecitabine or an anti–epidermal growth factor receptor agent, like cetuximab, remain considerations in this challenging case.

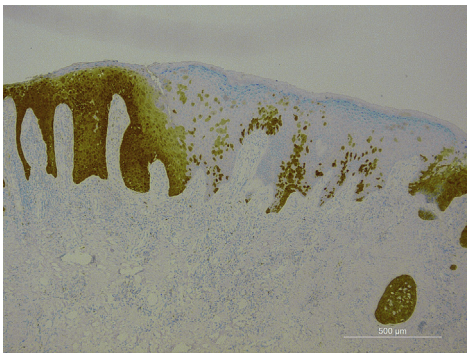

Fig 2. Positive p16 immunohistochemistry within the underlying dysplastic epithelium.

DISCUSSION

Genital SCCIS can be challenging to diagnose. With potentially fewer morphologic clues than at other anatomic sites, eczematoid or psoriasiform mimickers are possible. Failure to respond to treatment should prompt biopsy and revisiting of the initial diagnosis. A review of the literature for male genital SCCIS uncovered 118 individual cases isolated to the skin with 11 further cases overlapping with cases in on the glans penis. Thirteen of these specifically implicated HPV infection as the inciting factor. In our patient's case, MGUS might have contributed to allowing malignant transformation of HPV-infected skin. MGUS carries a 1.5 times greater risk of nonhematologic malignancies.[5] MGUS-associated immunosuppression likely led to the extent and progression of his disease. A negative

Table I. Summary of the effectiveness of treatments for Bowen disease

Treatment	Complete response (%)	Recurrence rate (%)[+]	Evidence in immunosuppressed patients
Cryotherapy (2 freeze-thaw cycles)	50-100[8]	10-36[8]	
Surgery			
Electrodesiccation	93-98[8]	9[8]	
Mohs micrographic surgery	95-98[10]	3-6[10]	
Topical 5-fluorouracil*	36-92[8]	11[8]	†
Imiquimod (5%)*	75-100[8]	0[8]	†
Diclofenac (3%)	Insufficient data	Insufficient data	
Radiation			
Traditional	94-100[8]	<1[8]	
Superficial	>99[9]	3-9[9]	
Ablative laser	>99[8]	20-26[8]	
MAL-PDT	84-93[8]	12-15[8]	†

The above is compiled from reviews and previous meta-analysis. The most effective therapies are reported. Combination therapy only slightly increased effectiveness of topical therapy.
MAL-PDT, Methyl aminolevulinate photodynamic therapy.
*Varies widely because of differences in protocols; improved response with longer duration dosing.
†Recurrence rates are reported for the end of all studies ranging from 2 to 5 years.

colonoscopy finding supports that his malignancy originated from the genital and gluteal skin.

Immunohistochemistry can suggest HPV-related SCCIS over other causes. The tumor suppressor gene $p16^{INK4a}$ is encoded by CDKN2A. HPV causes overexpression of p16 and inactivation of pRb, resulting in unregulated cell cycle progression. Expression of p16 has been noted in the majority of cases of SCCIS.[6] Recently, HPV-associated SCCIS was found to have a $p16^{+}$, Rb^{-}, $p53^{-}$ molecular signature.[6,7] It is unclear whether identifying this pattern on pathologic specimens would predict clinical response to therapy with imiquimod, which promotes antiviral cytokines. Positive p16 status did not predict response in our patient.

Choice of treatment is guided by the tumor properties (size and thickness), the patient's immune status, and desire for a cosmetic outcome. A range of treatment options are listed in Table I. In our patient, extensive disease precluded surgical intervention and cryotherapy. Laser and photodynamic therapy were limited by cost. Based on published reports,[8] 5% imiquimod cream was chosen, as it is the most effective topical therapy compared with 5-fluorouracil (75% to 100% vs 36% to 92% complete response) with the lowest recurrence rate (0% vs 11%). Diclofenac gel has little data to assess its true efficacy, although benefit was shown in a case series for SCCIS.[9] If vital structures can be preserved, radiotherapy is a viable option with good cosmetic outcome.[8,10] Superficial radiotherapy (SRT), given its lower toxicity, can be a helpful for patients compared to traditional radiation. The recurrence rate is 3-9% for superficial radiotherapy.[10] Systemic chemotherapy and anti–epidermal growth factor receptor treatment are reserved for refractory cases. Few case reports exist.

CONCLUSION

Genital SCCIS can mimic common dermatoses like psoriasis and requires a tailored therapeutic approach. This unusually extensive case highlights the potential role of HPV in SCCIS, the impact of concomitant immunosuppression, and the need for an expanded therapeutic armamentarium in this disease.

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