



Imiquimod treatment of vulvar melanoma in situ invading the urethra

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ABSTRACT

The primary treatment of both in situ and invasive vulvar melanoma is wide local excision of the primary neoplasm. However, this can be a surgical challenge for size, multifocal presentation with proximity to urethra or anus and tendency for local recurrence. The data on adjuvant therapy for vulvar MIS is very limited.

A 69-year-old patient with melanoma of the vulva underwent a simple vulvectomy with positive margins in peri-clitoral area, followed by modified radical vulvectomy and bilateral inguinofemoral sentinel lymph node dissection with negative margins. She was later diagnosed with MIS of the vulva on different locations and had multiple wide local excisions over several years. One lesion was close to the urethra and a complete excision was difficult. Topical imiquimod × 16 weeks (5% cream) was given. The regimen was augmented from 3 to 5 times weekly. Complete resolution was found at 16 weeks and patient was disease free for 4 years. Recently however, a vaginal melanoma was detected.

Imiquimod appeared to be beneficial in the treatment of melanoma in situ of the vulva/ vagina when surgical options were not feasible producing local control of disease with the remaining risk for local and distant metastasis. Metastasis can appear years later, therefore long-term follow-up of patients treated with topical imiquimod is needed.

1. Introduction

Vulvar melanomas while arising from the skin are more similar to melanoma from mucosal sites and unlike cutaneous melanomas have no predisposing risk factors. It is unknown what percentage of vulvar melanoma in situ actually progresses to invasive melanoma but it is not uncommon to find melanoma in situ at resection margins for invasive melanoma (Brand et al., 1989). Mucosal melanomas tend to occur in older adults (>60 years of age) (Leitao et al., 2014; Sugiyama et al., 2007; Wohlmuth et al., 2020), are more common in women, and are more likely to be multifocal (20% vs 5%) than cutaneous melanomas. They also have a higher tendency for local recurrence, and regional and distant metastasis. Melanoma in situ (MIS) presents as a pigmented lesion of the vulva which is indistinguishable from more common benign lesions such as simple melanosis. In most cases there is asymmetric pigmentation with variegated color and indistinct borders. Biopsy is critical for diagnosis. The primary treatment of both in situ and invasive vulvar melanoma is wide local excision of the primary neoplasm with 1–2 cm negative margins. However, this can be a surgical challenge as many of these neoplasms present at a relatively larger size, are often multifocal and have proximity to urethra and anus (Leitao et al., 2014; Sugiyama et al., 2007).

The data on adjuvant therapy for vulvar MIS is very limited and cannot necessarily be extrapolated from skin melanomas. A promising

newer approach is immunotherapy which is targeting the body's own immune system to fight the cancer via T-cell stimulation. Treatment of metastatic melanoma has been revolutionized by immunotherapy. Both drugs that target programmed cell death protein 1 (PD-1) and anti-cytotoxic T-lymphocyte antigen (CTLA) have resulted in significant improvements in overall survival. Imiquimod is a topical immune response modulator that has both antiviral and antitumor activity. It has been used to treat genital warts and squamous intraepithelial lesions of the lower genital tract. Safety and efficacy in treating melanoma in situ is unknown. Imiquimod is still considered an experimental approach with only a few cases reported for treatment of vulvar melanoma/ melanoma in situ (MIS). We report a case of a recurrent vulvar MIS with involvement of the urethra which was successfully treated with topical imiquimod for 16 weeks.

2. Case presentation

The patient was originally diagnosed with invasive vulvar melanoma in the clitoral area in 2004, at the age of 69 years. She initially underwent a simple vulvectomy, then was found to have a persistent vulvar melanoma in the periclitoral region and needed a modified radical vulvectomy and bilateral inguinal/femoral sentinel lymph node dissection. Pathologic evaluation revealed invasive melanoma with negative margins and no lymph node metastasis. The vulvar melanoma was

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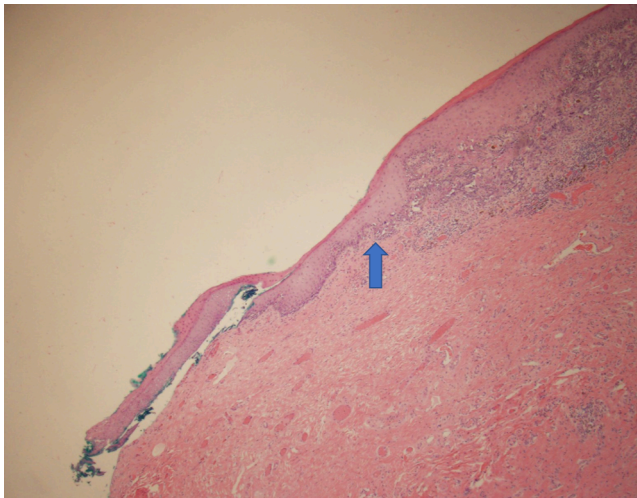


Fig. 1a. Periurethral MIS with margin, lower magnification. Low power photomicrograph of melanoma -in-situ. On the left is normal squamous mucosa with blue ink marking the margin. Arrow marks edge of proliferation of atypical melanocytes at the dermal-epidermal junction and extending into the epidermis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

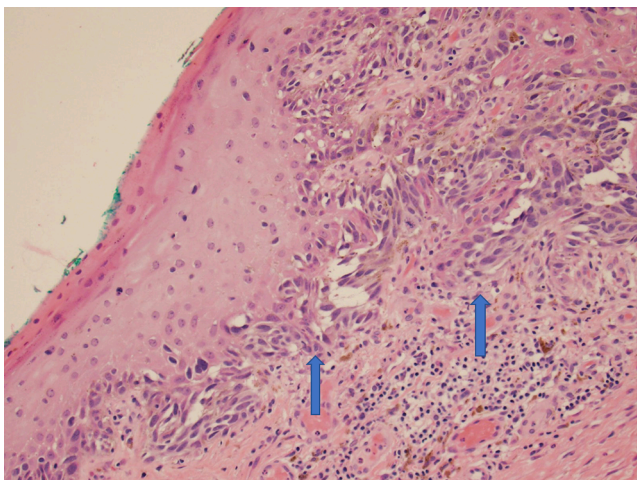


Fig. 1b. Periurethral MIS, higher magnification. Arrows mark proliferation of atypical melanocytes and dermal-epidermal junction and extending into the epidermis. Inflammation and phagocytic histiocytes are in dermis but no invasive melanoma.

preceded by the resection of an invasive cutaneous melanoma on her left thigh a year earlier. The patient is of Ashkenazi Jewish descent, and her mother has a history of invasive melanoma. Genetic testing was performed and no deleterious mutations were identified. She was followed by both Gynecologic Oncology and Dermatology. Over the years, she developed focal hyperpigmented vulvar lesions which were managed with multiple partial vulvectomies. The pathology reports from the excisions in 2010, 2011 and 2015 showed melanoma in situ (MIS) either approximating or involving peripheral margins but the deep margins were always free. In 2015, at the time of multi-focal resections, she had scattered areas of MIS involving her vulva but no evidence of invasive melanoma. All lesions were grossly excised at that time. However, one year later in 2016, she was found to have new lesions in the superior portion of her vulva extending to the level of the urethra. Surgical resection with an attempt to get negative margins was attempted and the pathology report showed extensive MIS approximating the margins at the urethra. (Fig. 1a and Fig. 1b)

The patient, now 81 years old, was offered various options in that the standard of care for melanoma in situ would be re-excision with likely sequela of incontinence or urinary conduit. Members of the Dermatology and Oncology Department were included in the discussion and offered imiquimod as a topical local treatment for MIS. Immune checkpoint inhibitors were discussed, but given her age and the fact that this was only melanoma in situ at this point in time, this option was not pursued.

Dermatology initiated the treatment with topical imiquimod as a local immunotherapeutic agent given institutional experiences of responses at other sites. The patient was aware of the anticipated local inflammation, as well as the potential for symptoms of systemic inflammation. It was discussed that some people react very quickly and vigorously to this medication and some very slowly, if at all. The patient began treatment with imiquimod 5% external cream to the vulva and urethra in October 2016. She began 3x/week, was closely monitored, and instructed to stop using the cream should she develop severe pain or ulceration. One month later, imiquimod 5%-use was increased to 5x/week with breaks on the weekends. Irritation of the vulva was interpreted as a sign that T-cells were being recruited to the local site. Other symptoms were burning with urination, but no hematuria. In February 2017, she completed a 16-week course of imiquimod 5%. She had significant redness and irritation on the vulva as well as some dysuria by the end of the course, but 10 days after treatment completion all the symptoms resolved. At that time, her exam showed post-inflammatory dull erythematous patches on the outer labia and medial aspect of residual labial folds. She was clinically followed every 3 months for surveillance and her external genitalia, especially the peri-urethral area, were without abnormal pigmentation. Her groins were without palpable adenopathy. After November 2018, she was followed every 6 months and was free of recurrence for 4 years. She had pelvic ultrasound imaging twice for postmenopausal bleeding. December 2020, she was found to have a vaginal lesion and some pigmentation near the urethra. A CT chest/ abdomen/ pelvis and a whole body PET-CT were obtained. A wide local excision of both areas was performed. Pathology revealed a 1 cm malignant melanoma in a background of MIS with uninvolved margins from the vaginal excision and focal atypical melanocytic proliferation suspicious for MIS with uninvolved margins in the periurethral area. The patient is currently receiving single agent nivolumab and tolerating it well.

3. Discussion

Imiquimod is an immune response modifier with antiviral and antitumoral activities. The predominant activity of imiquimod is mediated through agonistic activity towards toll-like receptors (TLR) 7 and 8, and consecutively, activation of nuclear factor-kappa B (NF- κ B). Pro-inflammatory cytokines, chemokines and other mediators are induced and antigen-presenting cells activated, leading to a profound T-helper (Th1)-weighted antitumoral cellular immune response. Another mode of action targets the adenosine receptor (AR) signaling pathways and causes reduction of adenylyl cyclase activity. Through suppression of a negative regulatory feedback mechanism which normally limits inflammatory responses, it augments the pro-inflammatory activity. At higher concentrations, imiquimod exerts some pro-apoptotic activity against tumor cells (Schön and Schön, 2007). Imiquimod was originally used for genital warts and has since been shown very effective in treatment of vulvar intraepithelial neoplasia (VIN), Paget's disease of the vulva, basal cell cancer, actinic keratosis and lentigo maligna of the skin. There are multiple case reports using imiquimod in MIS of the skin (Ellis et al., 2012). Imiquimod appears to be beneficial in the treatment of melanoma in situ of the skin when surgical options were not feasible.

Vulvovaginal melanomas are biologically more similar to mucosal melanomas than cutaneous melanomas and there are only rare case reports in the literature that describe the experimental approach of imiquimod use for vulvar or urethral melanoma/ MIS. Prescott

Table 1
Case reports of treatment of vulvovaginal MIS with imiquimod.

Paper	Original diagnosis, surgery and resection margins	Progression	Further treatment and outcome
Prescott et al	68 yo with malignant melanoma, mucosal lentiginous type near left hymenal ring, wide local excision performed and margins positive for MIS Wide radical excision with inguinal sentinel lymph node dissection for MIS; margins positive for MIS but lymph nodes negative	4 months MIS on left and right hymenal ring, right vulva	Topical imiquimod Complete resolution NED 18 months
Lonsdale-Eccles et al	68 yo with multifocal MIS on left labia minora, skinning vulvectomy (2 mm margins) and margins positive (possible areas of invasion) Skinning vulvectomy for MIS with initially positive margins but re-excision performed via Mohs to negative margins	4 years MIS, suspicious for invasive melanoma under clitoral hood	'Skinning' vulvectomy followed by mohs, then topical imiquimod Complete resolution NED 18 months
Sadownik et al	72 yo with MIS on vestibule, wide local excision with positive margins Patient declined further surgery	3 months lentiginous MIS inside right labia minora and peri-urethral	Topical imiquimod x 6 weeks NED at 10 months
Smyth et al	75 yo with multifocal invasive melanoma of vulva, modified radical vulvectomy + bilateral inguinofemoral lymphadenectomy with margins and lymph nodes negative	5 months Melanoma in unspecified vulvar location	Topical imiquimod Resolution of pigmentation within 6 months of imiquimod initiation but metastatic lung nodule 16 months later
Smyth et al	53 yo, with melanoma of right vagina, resection of right sided vaginal mass + sentinel lymph node dissection for melanoma with margins and lymph nodes negative	7 years Melanoma in unspecified vulvar location	Topical imiquimod Complete resolution after 7 weeks, however micro-metastatic disease 6 months later in 2 pelvic lymph nodes which were removed NED at 10 years from original diagnosis
Fuchs et al	69 yo with melanoma of vulva, simple vulvectomy with	6 years Followed by MIS on vulva,	Multiple wide local incisions, then

Table 1 (continued)

Paper	Original diagnosis, surgery and resection margins	Progression	Further treatment and outcome
	positive margins in periclitoral area followed by modified radical vulvectomy and bilateral inguinofemoral sentinel lymph node dissection with negative margins	different locations including peri-urethral, multiple excisions over several years	topical imiquimod × 16 weeks Complete resolution at 16 weeks and disease-free × 4 years but recently vaginal melanoma detected

Legend: NED, no evidence of disease.

presented the case of a patient with recurrent vaginal melanoma in situ (Prescott et al., 2012); (Table 1). The anatomic location of the MIS recurrence around the hymen and vulva made a resection difficult and imiquimod was applied 3x weekly for 16 weeks with the patient being disease free at 18 months follow-up. Smyth (Smyth et al., 2011) presented two cases of locally recurrent mucosal urogenital invasive melanoma with topical imiquimod. One patient had recurrent vulvar melanoma, and imiquimod led to almost complete clinical resolution of pigmentation with the exception of the peri-urethral area where a biopsy confirmed persistent MIS. This patient subsequently developed pulmonary metastasis. The second patient in this study had a vaginal melanoma with several recurrences. After multiple excisional procedures, imiquimod was initiated with resolution of the abnormal area of pigmentation in the vagina. She was later found to have micro-metastatic disease in two pelvic lymph nodes that were laparoscopically removed but was reported disease free for a decade thereafter. Lonsdale-Eccles (Lonsdale-Eccles et al., 2006) reported successful treatment of a patient with vulvar melanoma in situ with topical 5% imiquimod cream. Sadownik (Sadownik and Crawford, 2010) published the case report of post-surgical treatment of melanoma in situ of the vulva with imiquimod. Three months after a wide local excision of MIS in the vestibular area, the patient presented with an early recurrence of mucosal lentiginous melanoma in situ in the periurethral area and inside the labium minus which was treated with imiquimod. The patient was clinically disease free at 10 months follow-up.

In these very limited examples, imiquimod appears to be beneficial for the treatment of MIS if surgical resection is not feasible. More experience is needed to determine efficacy and safety of this approach.

CRedit authorship contribution statement

Esther Fuchs: Writing – original draft. **Anisha Khanijow:** Visualization. **Rochelle L. Garcia:** Visualization, Writing – review & editing. **Barbara A. Goff:** Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Written informed consent was provided for this case report and is available upon request.

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