

Topical Treatment of Vaginal Melanoma
in situ with Imiquimod (Aldara®)Charles RBW^{1*}, Van de Vijver KK², Hermans RHM³ and Lok CAR¹¹Department of Gynecologic Oncology, Center of Gynecologic Oncology Amsterdam, The Netherlands²Division of Diagnostic Oncology & Molecular Pathology, The Netherlands Cancer Institute, Antoni Van Leeuwenhoek Hospital, The Netherlands³Department of Gynecologic Oncology, Catharina Hospital Eindhoven, The Netherlands

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*Corresponding author

Charles RBW, Department of Gynecologic Oncology, Center of Gynecologic Oncology Amsterdam, The Netherlands, Tel: +597442222 (or) +5978574448; Email: rcharles@azp.sr (or) charlesregillio@yahoo.com

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Abstract

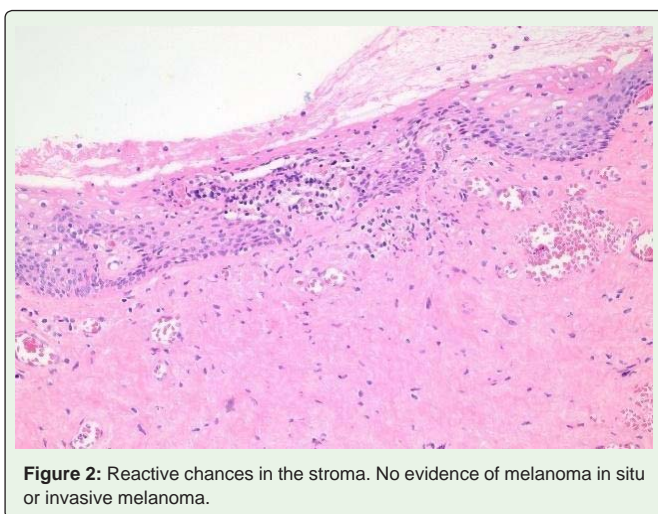
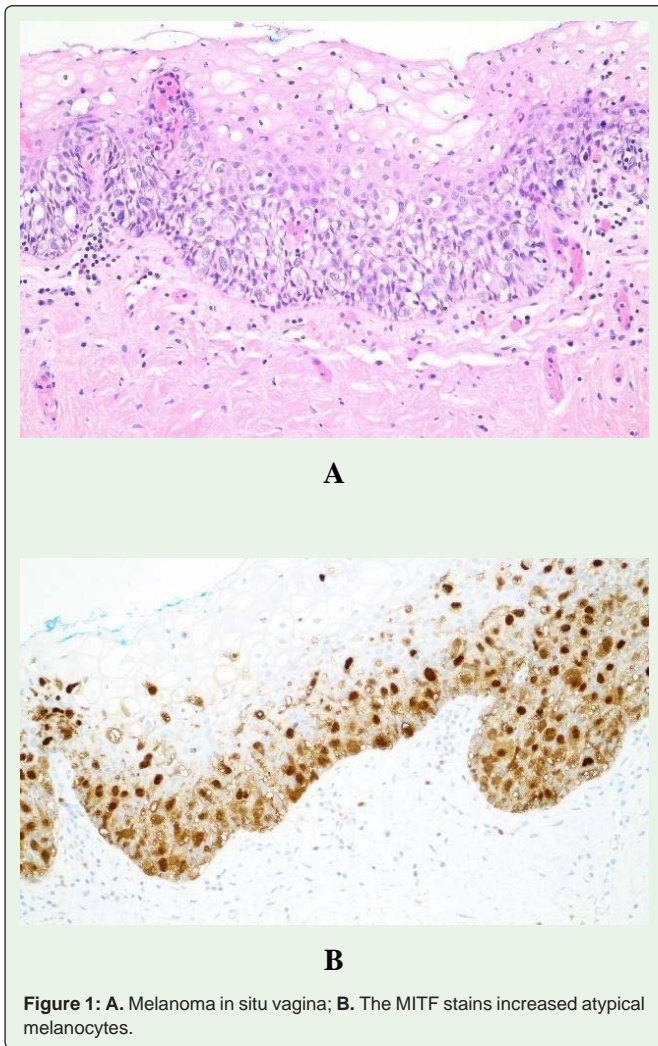
Melanomas of the vulva and vagina comprise less than 2% of melanomas in women and the overall prognosis is poor. Imiquimod (Aldara®) cream has shown to be effective in non-gynecologic cases of melanoma *in situ* but is less frequently used in gynecologic cases. We report a case of vaginal melanoma *in situ* treated with imiquimod. The usual treatment of vaginal melanoma *in situ* and vaginal melanoma is surgery. There are only a few case reports in the literature that show the effect of treatment of vaginal and vulvar melanoma *in situ* with imiquimod.

Introduction

Melanomas of the vulva and vagina comprise less than 2% of melanomas in women and the overall prognosis is poor [1]. Depending on the location of the lesion, radical surgery has traditionally been the mainstay of treatment [2]. There is little data regarding the use of topical agents for treatment of vaginal melanoma and melanoma *in situ*. Imiquimod (Aldara®) cream has shown to be effective in non-gynecologic cases of melanoma *in situ* [3,4] but is less frequently used in gynecologic cases. In the literature there are only two case reports which describe the successful treatment of recurrent vaginal melanoma *in situ* with imiquimod [5,6]. We report a case of vaginal melanoma *in situ* treated with imiquimod.

Case Report

A 58-year-old woman presented with a cervical melanoma *in situ*. She underwent a radical hysterectomy with pelvic lymphadenectomy. Histological examination demonstrated a multifocal lentiginous melanoma *in situ* with a linear extension of 5 mm and 2.7 mm in the cervix. However, melanoma *in situ* was seen reaching into the surgical margins of the vaginal manchet. Lymph nodes, ovaries, fallopian tubes and endometrium were negative for malignancy (*in situ*) and there was no vascular space invasion. Postoperative course was uncomplicated. Because of the unexpected finding of vaginal melanoma *in situ*, a vagina mapping under general anesthesia was performed. In all biopsies (n=15) melanoma *in situ* was found. Because of the risk of developing an invasive mucosal melanoma with poor prognosis the recommended treatment was colpectomy with reconstruction of a neovagina. Positron Emission Tomography (PET) scan showed no evidence of metastatic disease. The patient had a strong wish to preserve the vagina and requested a second opinion. She was therefore evaluated in a referral cancer center. Pathological review confirmed melanoma *in situ* in all vaginal biopsies (Figure 1). No invasive melanoma was found. The preferred treatment was still colpectomy, but a trial of local therapy with imiquimod was considered safe. Therefore, after extensive counseling, topical treatment with imiquimod was initiated followed by vaginal mapping 3 months after completion of therapy to evaluate treatment. If vaginal mapping would have shown melanoma or melanoma *in situ*, colpectomy would be the subsequent treatment. The patient was treated with imiquimod crème 50 mg/g, which she applied twice a week with a tampon to the affected area for three months. Side effects were vaginal pain, vaginal bleeding, discharge and itching. Because of the intense burning sensation and vaginal pain she could not apply imiquimod for one week. Overall, the treatment was tolerated. After completion of the therapy, pelvic examination revealed no abnormalities. The vaginal mapping under general anesthesia was uncomplicated. Pathological examination showed no evidence of melanoma *in situ* or invasive melanoma in any of the biopsies (n=22) (Figure 2). The patient is now closely monitored for 6 months without signs of recurrence.



Discussion

There is limited data on the natural course of vaginal melanoma *in situ*. The usual treatment of vaginal melanoma *in situ* and vaginal

melanoma is surgery. In non-gynecologic cases of melanoma *in situ* the use of non-surgical intervention, such as imiquimod, may be effective and may be considered in selected cases where surgery is contraindicated. There is little evidence so far to support the use of imiquimod as a neoadjuvant therapy [7]. In a systematic review of Tzellos et al. showed that those patients treated with imiquimod alone, 59% had a complete response at 5 months [7].

Imiquimod is a nucleoside analogue of imidazoquinoline family and belongs to a group of drugs called immune response modifiers. Schon et al. describes three main pathways through which imiquimod works [8]. The first is through agonistic activity towards toll-like receptors (TRL) 7 and 8 (on macrophages, dendritic cells and neutrophils cells), and consecutively, activation of nuclear factor-kappa B. The result of this activity is the induction of pro-inflammatory cytokines, chemokines and other mediators leading to activation of antigen-presenting cells and other components of innate immunity and, eventually resulting in a T-helper mediated antitumor response. The second is the interference of imiquimod with adenosine receptor signaling pathways, and the compound causes receptor-independent reduction of adenylyl cyclase activity. This mechanism may augment the pro-inflammatory activity of the compound through suppression of a negative regulatory feedback mechanism which normally limits inflammatory responses. Finally, imiquimod induces apoptosis of tumor cells at higher concentrations.

Side effects of imiquimod include local inflammatory reactions like blisters, a burning sensation, bleeding of treated area, swelling, stinging, pain in the treated area, skin redness, dry skin, itching, skin breakdown, skin crusting or scabbing, skin drainage, skin flaking or scaling, skin ulceration, sores, as well as systemic reactions like fever, “flu-like” symptoms, headache, and tiredness. Imiquimod is a patient-applied cream prescribed to treat genital warts, basal cell carcinoma and actinic keratosis. It has also been tested for treatment of Vulvar Intraepithelial Neoplasia (VIN) and Vaginal Intraepithelial Neoplasia (VAIN) with excellent responses [9].

There are only a few case reports [5,10,11] in the literature that show the effect of treatment of vaginal and vulvar melanoma *in situ* with imiquimod. Because of the lack of randomized controlled trials or guidelines, treatment regimens varied between these cases. Lonsdale-Eccles et al. [10] reported a case of a 68-year patient with multiple recurrences of vulvar melanoma *in situ* treated with topical imiquimod for 4 months with a complete clinical response and no evidence of disease in 18 months of follow up. Smyth et al. [5] reported the use of imiquimod in a 75-year-old woman with vulvar melanoma *in situ* who had a complete clinical response after 4 months of therapy. In the 14-month follow up there were no signs of disease. Finally, Lauren et al. [6] reported a case of a 68-year-old woman with recurrent vaginal melanoma *in situ* successfully treated with topical imiquimod 5% cream for a total of 4 months without evidence of recurrent melanoma *in situ* in the 18 months of follow up. All the treatments were well tolerated.

We can now add our case of vaginal melanoma *in situ* after treatment with cervical melanoma *in situ* successfully treated with imiquimod for a period of 3 months. These limited data show that topical imiquimod treatment for patients with vaginal melanoma *in situ* is feasible, but still needs to be considered an experimental treatment that can only be applied under strict surveillance.

Recently the patient was diagnosed with a recurrence of vaginal melanoma *in situ* and was treated by surgical removal of the lesion (colpectomy). With this additional information we can conclude that imiquimod is just a temporally treatment of vaginal melanoma *in situ*.

Informed consent

Informed consent was obtained from the patient for publication of this case report and accompanying images.

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