

Topical Imiquimod for Management of Recurrent Lentigo Maligna Melanoma *in Situ*

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ABSTRACT Topical imiquimod is a medication approved for the treatment of external genital and perianal warts, actinic keratosis, and superficial basal cell carcinoma. There have also been reports of its successful use in patients with lentigo maligna melanoma *in situ*. An 80-year-old female patient was diagnosed with lentigo maligna melanoma *in situ* which was then surgically removed. After several recurrences, nonsurgical treatment using topical 5% imiquimod was introduced. At 9-month follow-up the skin was completely healed with no evidence of cancer recurrence. In select cases, topical imiquimod seems to be an effective alternative to surgical treatment of melanoma *in situ* (MIS). Further studies are necessary to assess the successfulness of this treatment method.

KEY WORDS: lentigo melanoma, imiquimod, nonsurgical therapy

INTRODUCTION

Imiquimod is a topical immunomodulator, the use of which has been approved for the treatment of external genital and perianal warts, actinic keratosis, and superficial basal cell carcinoma (1). A growing number of reports also describe its use in treatment of melanoma *in situ* (MIS) (2-4).

Lentigo maligna is the most prevalent presentation of MIS. It typically occurs on sun-exposed parts of the body such as the face, head, and neck usually in older people with 65 years as the mean age at presentation (4). If left untreated, it slowly grows over the course of several years with a high risk of evolving into an invasive melanoma termed lentigo maligna melanoma, which shares the same prognosis as other types of invasive melanoma (4-6). Current guidelines suggest wide excision with 5 mm margins (6,7). However, there are cases when the size or location of the lesion preclude a surgical approach. Radiotherapy is

recommended in such cases. When both surgery and radiotherapy are not appropriate or refused, topical imiquimod is the recommended treatment. Cryotherapy and laser therapy are not recommended for the treatment of lentigo maligna melanoma *in situ* (4,6).

We present a case demonstrating the efficacy of topical imiquimod in the treatment of recurrent lentigo maligna melanoma *in situ*.

CASE REPORT

An 80-year-old woman with no medical history related to dermatologic or oncological diseases visited the dermatologist in March 2013 with a non-raised, pigmented lesion on the left part of the forehead. She reported the lesion had grown and changed color the over a period of 5-7 years. The same lesion had previously been diagnosed by her general practitioner as senile lentigo. At presentation, the lesion measured



Figure 1. Lentigo maligna melanoma on the forehead at the first visit at our outpatient clinic.

4.3×2.4 cm and had a brown pigmentation with small black areas (Figure 1).

After surgical consultation with the patient, a partial excision under local anesthesia was performed in April 2013. The specimen was sent to the pathologist. The final pathological analysis confirmed our clinical diagnosis of lentigo melanoma or MIS without intensive growth (Figure 2). Excision of the remaining part of the lesion followed in November 2013. Pathohistological examination showed that the margins were free of tumor cells.

A follow up examination in September 2014 revealed partial recurrence of the lesion, and another excision was performed. Pathohistological examination showed clear margins once again.

At the follow up examination in June 2018, the lesion was discovered to be growing again after a three-year remission. In October 2018, we discussed

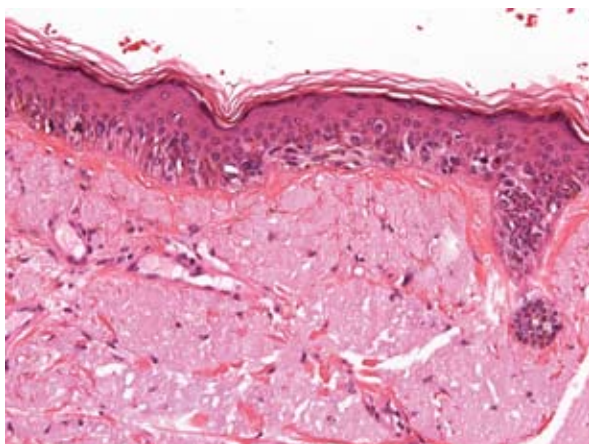


Figure 2. Histopathological examination revealed an increased number of atypical melanocytes forming nests at the dermo-epidermal junction as well as melanoma cells. Typical picture of lentigo maligna melanoma with no invasion.

surgical and non-surgical options with the patient. Due to the patient's advanced age and her desire to avoid another surgery and radiotherapy, treatment with 5% topical imiquimod was initiated. Imiquimod cream was prescribed 6 days per week once daily, followed by a 1-day interval without treatment. After 6 weeks of treatment the reaction was very strong, presented as an erythematous superficial ulcer covered with an eschar (Figure 3).

The patient was asked to cease use of imiquimod and instead commence daily application of a salicylic acid and betamethasone ointment. At the 1-week follow-up visit, the inflammation had subsided and the scab had come off (Figure 4).

At the 2-month follow-up visit we observed complete regression of the cancerous part of the lesion. Surrounding erythema was minimal.

At the 9-month follow-up examination the skin was healed. There was no evidence of lentigo maligna recurrence (Figure 5).

DISCUSSION

Imiquimod belongs to a class of drugs referred to as imidazoquinolines. It directly brings about apoptosis in tumor cells by facilitating an increase in caspase activity and up-regulating proapoptotic proteins such as Bax and Bak. Its indirect effect is triggered by binding to toll-like receptors on macrophages, neutrophils, and dendritic cells which causes an increased release



Figure 3. Strong reaction after week 6 of imiquimod topical treatment. An erythematous superficial ulcer covered with an eschar.



Figure 4. Regression of the reaction to imiquimod treatment due to use of betamethasone-containing ointment.

of inflammatory cytokines, most notably interleukin (IL)-12, tumor necrosis factor (TNF)-alpha and interferon alpha. These in turn increase the number of natural killer cells and cytotoxic lymphocytes which attack malignant cells (1). Topical use of imiquimod is FDA approved for the treatment of genital human papillomavirus, actinic keratosis, and superficial basal cell carcinoma (1,4,8). Studies have also reported its use in the treatment of lentigo melanoma (4,5).

Current guidelines suggest surgical excision with 5 mm margins as the mainstay treatment for lentigo maligna melanoma *in situ* (6,9). However, studies have shown that 5 mm margins are often inadequate. Kunishige *et al.* reported that 5 mm margins cleared only 86% of MIS margins, while 9 mm margins were successful in 98.9% of interventions (9). Another study showed that 5 mm margins were only sufficient in 42% of cases (10). In case surgery is not possible or is refused, radiotherapy is the treatment of choice. When both surgery and radiotherapy are not appropriate or refused, topical imiquimod is the recommended treatment. Cryotherapy and laser therapy are not recommended for the treatment of LM (4,6).

Histological examination of lentigo maligna melanoma *in situ* reveals the following typical features: hyperplasia of atypical melanocytes at the dermo-epidermal junction, confluence of atypical melanocytes, and occasionally pagetoid spread (11). Atypical melanocytes can therefore extend beyond the clinically obvious borders of lentigo maligna melanoma *in situ*. These atypical cells can then blend with surrounding sun-damaged skin, resulting in the need to increase margins in order to prevent local recurrences. This is known as the field change effect (4).

One of the earliest case reports using 5% imiquimod cream to treat lentigo maligna melanoma *in situ*



Figure 5. Complete regression of lentigo maligna melanoma 9 months after treatment completion. No effect on seborrheic keratosis.

was published in 2000 by Ahmed and Berth-Jones. The patient was an 88-year-old man with a large lesion on the scalp that was treated for 7 months, 3 times a week (2,4). Treatment resulted in a complete clinical and histological cure. The patient was followed up for 9 months without signs of recurrence (2).

A similar case was reported in 2012 by Ellis *et al.* After 4 surgeries with persisting positive margins, an 82-year-old man with LM on his right cheek was treated with topical 5% imiquimod cream for 3 months. No clinical signs were present several months after the conclusion of the treatment (5).

In 2015, Fan *et al.* reported the case of a 75-year-old woman with MIS on her left cheek. Nonsurgical treatment was proposed after 2 surgeries with persisting positive margins. Imiquimod was used 5 times per week once daily. After a month, an erythema with central eschar was observed around the incision. Use of imiquimod was decreased to 3 times per week for 12 weeks. At the 4-month follow-up the erythema had almost completely subsided. Nine months after treatment there was no clinical evidence of persisting MIS (4).

In our case, 5% imiquimod cream was applied for 6 days per week once daily, followed by a 1-day interval without treatment. This short therapy resulted in total disappearance of the lentigo maligna lesion. After a period of 9 months there was no sign of recurrence.

Our case shows that even a shorter therapy with 5% imiquimod can be effective and there may be no need for longer therapy, which can bring major discomfort to the patient.

CONCLUSION

Imiquimod appears to be an effective form of treatment for MIS in selected cases when surgical options are not feasible. However, more case reports with longer follow-up periods may be required to further justify the use of immunomodulators such as imiquimod.

ETHICS

The study protocol was approved by the Local Ethics Committee which follows the guidelines set by the Helsinki declaration.

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