CASE REPORT

EXPERIMENTAL ONCOLOGY

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V. De Giorgi [1,*], B. Zuccaro [1], F. Silvestri [1], F. Venturi [1], J. Colombo [1], L. Trane [2]

[1] Section of Dermatology, Department of Health Sciences, University of Florence, Florence 50121, Italy
[2] Cancer Research "AttiliaPofferi" Foundation, Pistoia 51100, Italy
* Correspondence: Email: vincenzo.degiorgi@unifi.it

RECURRENT LENTIGO MALIGNA: CONSERVATIVE CONTINUOUS TREATMENT WITH IMIQUIMOD OR REPEATED SURGERY? A LONG-TERM FOLLOW-UP DERMOSCOPIC CASE STUDY

A case of recurrent lentigo maligna in a 45-year-old woman is presented. The disease relapsed several times following the surgical excision of the lesion. An alternative treatment with imiquimod 5% cream was then used. After 4 years of follow-up from the last surgery, this treatment achieved total clearance of the lesion. The problems of lentigo maligna diagnosis and treatment are discussed.

Keywords: lentigo maligna, melanoma, dermoscopy.

A 45-year-old woman presented in 2007 with a 2-year history of a flat, slow-growing asymptomatic lesion in the right malar region that had previously been treated by a dermatologist as a suspected seborrheic keratosis. Two electrocoagulation sessions were performed, but not a histopathologic exam. We completed a cutaneous examination, revealing a large, erythematous, poorly pigmented macula with asymmetrical borders within the scar of an electrocoagulation treatment. Dermoscopy of the lesion showed asymmetric pigmented follicular openings, grey circles, grey dots, and red areas (Fig. 1). These dermoscopic features led to the suspicion of lentigo maligna (LM); therefore, a skin biopsy was taken from the darkest area, and histopathology confirmed the suspicion. The lesion was subsequently completely surgically removed about 10 mm from the dermoscopic margins of the lesion, and the final histological diagnosis was LM melanoma. The tumor thickness was 0.7 mm (pT1a according to AJCC 2018), and the surgical margins were clear. Chest radiography and various ultrasound examinations (at the abdomen

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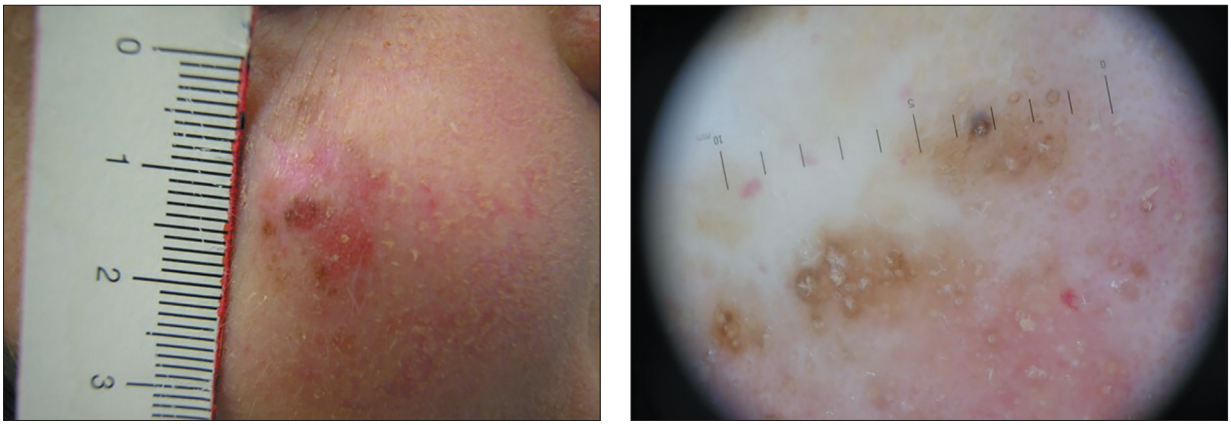
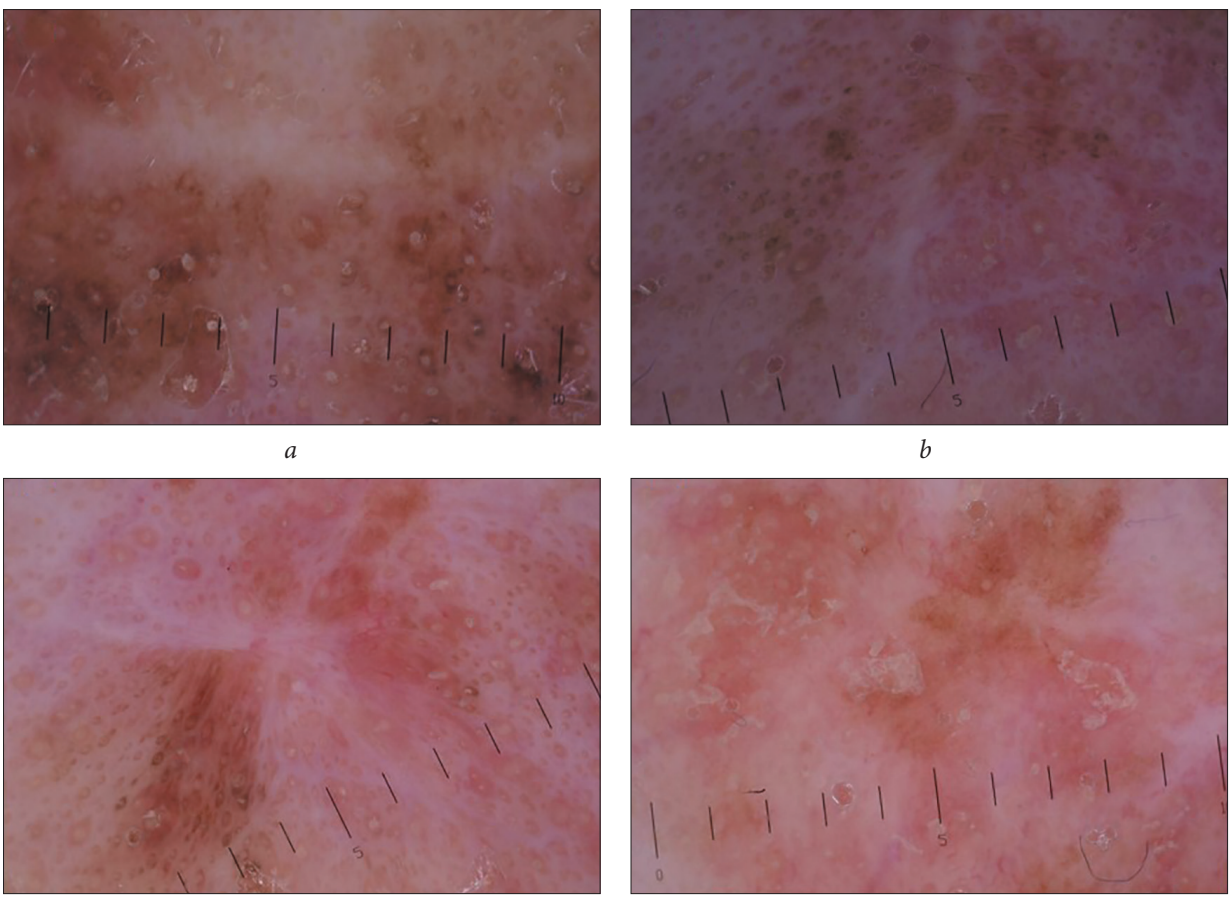


a *b*

Fig. 1. The right malar region of a 45-year-old woman: *a* — Clinically, the macula is large, erythematous, and poorly pigmented with asymmetrical borders within the scar of the previous electrocoagulation treatment; *b* — Dermoscopically, typical asymmetric pigmented follicular openings, grey circles, grey dots, and red areas can be seen



a *b*

c *d*

Fig. 2. Dermoscopic images of the various relapses of lentigo maligna in the right malar region of a 45-year-old woman. All dermoscopic parameters were typical of lentigo maligna: *a* — 2010; *b* — 2015; *c* — 2016; *d* — 2017

and locoregional lymph nodes) were performed, all of which were negative for the presence of disease.

In 2010, three years after surgery, pigmentation reappeared on the scar. Dermoscopic examination led to the suspicion of classic asymmetric pigmented follicular openings typical for LM (Fig. 1, *a*). The new lesion was surgically removed, and histopathological examination confirmed the dermoscopic diagnosis of LM with disease-free margins. The disease relapsed again in 2015, 2016, and 2017, always with pigmentation that appeared on the scar of prior surgery (Fig. 2). All relapses were surgically excised about 5 to 7 mm from the lesion margin, and histology was used to confirm each diagnosis (confirmed LM, hence non-invasive melanomas) and showed negative margins. After the fourth surgical removal, LM recurred again in 2018. At that time, a different strategy was chosen due to the risk of disfigurement. Based on physicians' personal experience and guidance from the literature, the proposed alternative treatment was imiquimod 5% cream applied once daily 5 times weekly for 6 weeks, repeated twice more at 30-day intervals (90 applications in total). The application area was at least 10 mm beyond the defined tumor margins. The patient adequately prepared for the possibility of local inflammatory reactions and tolerated the therapy well despite erythema, edema, and discomfort, most pronounced after the first cycle. Follow-up was performed every 4 months.

After 4 years of follow-up from the last surgery, this treatment achieved total clearance of the lesion, confirmed via clinical and dermoscopic examinations.

Discussion

Lentigo maligna is a slow-growing in situ form of melanoma that typically occurs on chronically sun-exposed skin such as the head and neck skin [1]. A differential diagnosis of facial lesions is very difficult, and a wrong diagnosis can also lead to important errors in subsequent treatments. In this case, the lesion was mistakenly diagnosed without histological examination as seborrheic keratosis and was therefore treated with diathermocoagulation. This case highlights the role of dermoscopy in the complex management of this disease. Dermoscopy in the presence of typical characteristics not only can support suspected LM but also be helpful in selecting the most appropriate area to biopsy [2, 3]. Moreover, it allows proper assessment of the margins, extending the clinically visible margins of the tumor by far. Finally, dermoscopy is always essential during follow-up to achieve an early diagnosis of relapse.

Left untreated, LM can evolve into an invasive form of lentigo maligna melanoma, but it is challenging to treat. The gold standard, suggested by current international guidelines, is the surgical removal with a margin of at least 5 mm. However, surgical management can present difficulties for various reasons: the lesion could be located close to critical anatomical structures, the macroscopic margins are often unclear, large lesions can require reconstructive procedures after excision, and most patients with LM are elderly, frail, and having comorbidities. Moreover, even with extensive surgery, histopathology often shows positive margins, the result of amelanotic subclinical extensions beyond the clinical margins and/or background actinic melanocytic hyperplasia. Even with clean margins, relapse risk remains high due to a sort of cancerization field, such as that occurring with actinic keratoses, where a certain number of atypical melanocytes are polluted and evolve. Swetter et al. [4] suggested that histological clearance should not necessarily be the gold standard to measure the success of LM treatment. All this could explain the high recurrence rates for LM, as seen in the present case. Mohs micrographic surgery allows for a more comprehensive examination of the margins. However, the published recurrence rate is estimated at 2% [5] due to the difficulties in

evaluating the margins on sun-damaged skin, particularly given that the definition of a positive margin remains debatable and some physicians believe that a single atypical melanocyte may be considered sufficient to indicate a compromised margin [6]. It is difficult, however, to predict the biological behavior of such single atypical melanocytes. The use of immunostaining with melanoma antigen recognized by T-cell (MART-1) can be helpful in such cases [7]. Regardless, Mohs surgery, even if it presents a lower possibility of recurrence, often leads to extremely extensive interventions in an extensive search for margins free from atypical melanocytes, though there is no certainty that they can actually progress.

Topical imiquimod is an immune response modifier approved for the treatment of actinic keratosis, superficial basal cell carcinoma [8], and external genital and perianal warts. Its effectiveness in the treatment of LM [9, 10] is provided by the ability to target atypical melanocytes both directly and indirectly, inducing pro-inflammatory cytokines including interferon alpha and tumor necrosis factor within the skin, possibly potentiating an immune response and inducing a cytotoxic T-cell-mediated immune response *in situ*. These factors could account for the destruction of malignant melanocytes in LM. This report confirms that imiquimod can decrease LM recurrence rates, avoiding disfiguring scars or functional impairment resulted from repeated surgical excisions. Moreover, dermoscopy is not only an indispensable tool for diagnosing and managing LM but also an important part of follow-up evaluations of lesions undergoing therapy with imiquimod, both to assess treatment response and to lend to the early diagnosis of a possible relapse. In fact, in the case of LM, the dermoscopic parameters allow a realistic evaluation of its evolution.

Therefore, although we have reported a single case, we propose that after one relapse of LM, treatment should be changed to topical imiquimod. We do so basing on our multidisciplinary experience and review of the literature. Alternatively, imiquimod can be used as an adjuvant therapy after surgery, particularly in the presence of background melanocytic dysplasia or close margins. The validity of this management plan must be confirmed by other cases with long-term follow-ups, aiming to facilitate optimal patient outcomes.

Imiquimod treatment requires careful management, and when correctly administered with appropriate monitoring and dermoscopic follow-up, it can achieve excellent outcomes. However, studies assessing the most efficient treatment scheme are required.

Author Contributions

Dr De Giorgi had full access to all data in the study and takes responsibility of data integrity and accuracy in the data analysis.

Study concept and design: De Giorgi,

Acquisition of data: Zuccaro, Colombo, Venturi, Silvestri,Trane

Analysis and interpretation of data: De Giorgi

Drafting of the manuscript: De Giorgi, Zuccaro, Colombo

Critical revision of the manuscript for important intellectual content:

De Giorgi,

Study supervision: De Giorgi

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Publication ethics

The patient described in this manuscript gave written informed consent to publication of her case details

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В. ДеДжорджи [1,], Б. Дзуккаро [1], Ф. Сильвестри [1], Ф. Вентури [1], Дж. Коломбо [1], Л. Тране [2]*

[1] Відділення дерматології, медичний факультет університету Флоренції, Флоренція, Італія
[2] Товариство досліджень раку "АттіліяПоффері", Пістойя, Італія

РЕЦИДИВНЕ ЗЛОЯКІСНЕ ЛЕНТИГО: КОНСЕРВАТИВНЕ ЛІКУВАННЯ ІМІКВІМОДОМ ЧИ ПОВТОРНЕ ХІРУРГІЧНЕ ВИДАЛЕННЯ? ТРИВАЛЕ СПОСТЕРЕЖЕННЯ: ВИПАДОК З ПРАКТИКИ

Представлено випадок рецидивного злоякісного лентиго у жінки віком 45 років. Рецидив відзначали кілька разів після хірургічного видалення. Застосовано альтернативне лікування іміквімодом у вигляді 5% крему. Впродовж 4 років після останнього хірургічного втручання рецидиву не спостерігали. Обговорюються проблеми діагностики та лікування цієї патології.

Ключові слова: злоякісне лентиго, меланома, дерматоскопія.