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CASE REPORT

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A case report and literature review of delayed telogen effluvium after topical imiquimod use in treating a cervical high-grade squamous intraepithelial lesion

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Abstract

The use of imiquimod in cervical intraepithelial lesions has been evaluated in different trials and was found associated with various and numerous adverse events. Telogen effluvium is an infrequent systemic adverse event observed mainly in patients experiencing severe systemic adverse reactions. This paper presents the case of a young woman who developed telogen effluvium after intravaginal imiquimod use that was not preceded by other systemic adverse events and resolved gradually after nine months. Telogen effluvium after intravaginal imiquimod use is rare, may appear without any preceding severe adverse event, and may persist for an extended period.

Keywords

Imiquimod; Intravaginal administration; Adverse effect; Telogen effluvium

1. Introduction

Although the introduction of cervical cancer screening programs has led to a significant drop in the incidence of cervical cancer, the incidence of precancerous cervical lesions is still relatively high. Precancerous cervical lesions are most commonly treated with excision (large loop excision of the transformation zone (LLETZ)), and despite the procedure being simple and highly efficient, it may cause long-term complications such as premature delivery in subsequent pregnancies [1]. Hence, various conservative treatment options are being explored in women of reproductive age, of which topical immunomodulator imiquimod is one of them [2]. Here, we present the case of a young woman who developed telogen effluvium after intravaginal imiquimod treatment and reviewed relevant literature on this topic.

2. Case report

A 24-year-old nulliparous patient, otherwise healthy, without a history of prescribed medications, allergies and abnormal uterine bleeding, no current use of contraceptives and a non-smoker, was diagnosed with a high-grade squamous intraepithelial lesion (HSIL) (cervical intraepithelial neoplasia—CIN 3). The patient had visited different treatment modalities for treatment suggestions, and because she was reluctant to undergo surgery, she accepted to participate in our ongoing study [3]. She started treatment at the beginning of May 2020, whereby imiquimod was used intravaginally using an applicator three times per week for 16 weeks (cumulative dose of 600 mg) based on the study protocol. A follow-up examination at our colposcopy unit in week 10 and week 20, along with active reporting of adverse events and filling out standardized questionnaires (European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) and cervical cancer-specific Quality-of-Life module (QLQ-CX24)).

At week 10, she reported mild vaginal bleeding, headache and vertigo (grade 1, based on the 5th version of CTCAE classification), which disappeared by week 20. At that time, she did not report any other side effects. At week 20, the treatment was considered successful due to regression of the lesion from CIN 3 to CIN 1. Six months after treatment completion, the patient reported a change in her hair structure and hair loss (Fig. 1) despite the symptoms starting about four weeks since the last application of imiquimod. She underwent a hair pull test and was tested positive. The patient also reported significant hair shedding while combing. She specifically stated that she did not have any other symptoms and had no known new acute or chronic illness. She took no other medications, was emotionally stable and experienced no major stressful events during this period. Then, she was prescribed dietary supplements (methylsulfonylmethane—MSM powder) and stopped dyeing her hair. Telogen effluvium persisted for nine months, after which her hair structure returned to normal and hair loss completely disappeared by May 2021.

Beforehand, written consent was obtained from the patient allowing the publication of this case report and all accompanying graphic material.

3. Discussion

The results of clinical trials indicated that although the treatment of cervical HSIL with intravaginal imiquimod (off-label

FIGURE 1. From left to right, the four pictures represent the state before, during, after, and nine months after the treatment with imiquimod. Substantial hair loss is principally noticeable in the third picture (approximately one month after the treatment).

use) is relatively successful, it is still inferior to standard treatment with LLETZ and might be associated with various side effects ranging from mild to severe [3–8].

Acute telogen effluvium is a form of diffuse, transient loss of a portion of hair resulting from an abnormal shift in follicular cycling that causes premature hair shedding [9]. Its occurrence might be triggered by various factors, including major illness, childbirth, emotional stress, nutritional changes, low levels of ferritin and vitamin D, drugs, medications, endocrine disorders, and inflammatory and infectious conditions [10–12]. In this case, telogen effluvium occurred four weeks after treatment completion with topical imiquimod and was not preceded by severe systemic symptoms. Therefore, other known causes of effluvium were excluded.

Based on a literature search, we identified only two articles related to localized hair loss after topical imiquimod treatment [13, 14]. The first study reported the case of a patient treated for actinic keratosis on the scalp, following which telogen effluvium occurred six weeks into the treatment. The second study described the case of two patients treated for HSIL, whereby one patient developed telogen effluvium one week after completing treatment (imiquimod cumulative dose of 262.5 mg) and lasted for seven months, while the other patient developed telogen effluvium toward the end of the 16-week treatment course (imiquimod cumulative dose of 250 mg) and lasted for two months. Systemic symptoms in both patients preceded the onset of hair loss. After reviewing all papers published in the English language (abstract at least) that report the use of intravaginal imiquimod for the treatment of CIN and vaginal intraepithelial lesions (VaIN) and excluding systematic reviews of literature and meta-analyses, 19 papers were identified and consisted of prospective and retrospective studies, case reports and case series [4–6, 15–30]. Altogether, they comprised of 532 patients (CIN, n = 361; VaIN, n = 99; CIN or VaIN, n = 72), of whom three were the aforementioned patients who experienced telogen effluvium. We found that substantial hair loss for several months was a clinically significant event that occurred at a young age. However, it was not possible to estimate the exact frequency of telogen effluvium.

Imiquimod is an immune modulator that acts at several levels of immune responses. Imiquimod is currently recommended for treating humanpapilloma virus (HPV) related verrucae, actinic keratosis and superficial basal cell carcinoma. Its synergistic actions are executed *via* different pathways, leading to antitumor effects, which consequently contribute to the destruction and eradication of HPV and HSIL [31, 32]. It was also reported to affect the interfollicular epidermis, but its effects on hair follicles and hair follicle stem cells were unknown [33]. Generally, when a drug is used topically, there is minimal systemic absorption. In the case of imiquimod, about 0.6% of the applied dose was observed in the urine of the studied subjects [34]. Currently, there is no data on the absorption of imiquimod through the vaginal mucosa; however, based on the data on estradiol absorption [35], we speculate that the absorption of imiquimod through the vaginal mucosa might be about 10–20 times higher than with transdermal application.

4. Conclusion

According to our experience and literature review, intravaginal off-label use of imiquimod might lead to systemic adverse events, among which telogen effluvium is rare but might occur for long durations. Therefore, the intravaginal use of imiquimod might not be appropriate outside clinical trial settings unless thorough communication with the patients about all possible systemic adverse events associated with the drug's off-label use.

AUTHOR CONTRIBUTIONS

AC and MP were responsible for collecting and analyzing the patient's data and drafting, editing and revising the manuscript. Both authors have read and approved the manuscript and ensure the authenticity of the case.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We obtained written consent from the patient allowing publication of the case report and all accompanying graphic material. Formal ethical approval was not sought as it was not deemed necessary given this was a review of clinical practice outcomes and informed consent had been sought.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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