Vismodegib-Induced Alopecia: Trichoscopic and Confocal Microscopy Evaluation

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Established Facts

- Hair loss is a typical late side effect of vismodegib usage and is reversible, but regrowth takes many months.

Novel Insights

- Vismodegib-induced alopecia has the same trichoscopic and RCM characteristics in both patients and resembles an alopecia areata and chemotherapy-induced alopecia. Vismodegib-induced alopecia is characterized by diffuse loss of hair density of the scalp. It is gradual and has a longer time to onset than that with cytotoxic chemotherapy, developing after at least 2 months.

Keywords

Alopecia · Confocal microscopy · Hair loss · Trichoscopy

Abstract

Introduction: Vismodegib is the first-in-class inhibitor of the sonic hedgehog pathway useful in the treatment of locally advanced or metastatic basal cell carcinoma (BCC) that is not amenable to surgery and radiation therapy. Common adverse events of vismodegib, probably mechanism related, include alopecia (58%) as a reversible side effect. **Case Presentation:** We report 2 cases of patients receiving vismodegib for the treatment of locally advanced BCCs that developed alopecia during treatment and describe clinical, dermoscopic, and reflectance confocal microscopy (RCM)

features of this adverse event. **Conclusion:** Alopecia is one of the most distressing adverse events leading to vismodegib discontinuations. To our knowledge, these are the first descriptions of RCM dermoscopy in vismodegib-induced alopecia. Trichoscopy and confocal microscopy are essential to monitoring vismodegib hair loss and the response to the treatment.

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Introduction

Basal cell carcinoma (BCC) is the most common malignancy that accounts for 80% of non-melanoma skin cancers [1]. BCCs are usually associated with a good

Fig. 1. **a** Trichoscopic evaluation highlights the presence of yellow dots (yellow circle), black dots (black circle), Pohl-Pinkus hair (red arrow), and hair's miniaturization. **b, c** RCM evaluation shows the presence of yellow dots (yellow circle) and a dilated follicular infundibula containing yellowish, amorphous material, surrounded by a thin, white collaret CIA dots (blue circle). RCM, reflectance confocal microscopy; CIA, chemotherapy-induced alopecia.

prognosis and a low metastatic potential, and they can be treated by various medical or surgical therapy. Nevertheless, some lesions if not treated, progress to locally advanced state or spread to distant sites (metastatic BCC). Vismodegib is the first-in-class inhibitor of the sonic hedgehog pathway (Shh) useful in the treatment of locally advanced or metastatic BCC that is not amenable to surgery and radiation therapy [2]. Common adverse events of vismodegib, probably mechanism related, include alopecia (58%), muscle spasms (71%), and dysgeusia (71%) [3]. Alopecia induced by vismodegib is a reversible side effect. According to the Common Terminology Criteria for Adverse Events version 4.0, hair loss less than 50% is considered grade 1 alopecia, where $\geq 50\%$ loss is considered grade 2 alopecia. Alopecia is a predictable adverse event of oncological therapy. It can be caused by chemotherapy, radiotherapy, or targeted and hormonal therapy. Targeted therapy and immunotherapy can cause immune-mediated alopecia such as alopecia areata (AA) and permanent alopecia, as well as paradoxically hypertrichosis and trichomegaly [4]. We report 2 cases of patients receiving vismodegib for the treatment of locally advanced BCCs that developed alopecia during treatment and describe clinical, dermoscopic, and reflectance confocal microscopy (RCM) features of this adverse event.

Case 1 is a 64-year-old woman affected by superficial BCC (15 cm maximum diameter) of the pubic region treated with 2 cycles of topical therapy with imiquimod with an unsatisfactory result. The patient started oral vismodegib therapy (150 mg daily) for 6 months until complete healing and began to manifest a grade 2 alopecia from the third month of treatment up to total alopecia after 2 months of discontinuation of the therapy when hairs started to regrow. After 3 months of vismodegib, trichoscopic evaluation highlighted the presence of yellow dots, black dots, broken hairs, and Pohl-Pinkus and hair's miniaturization (Fig. 1a). Confocal microscopy showed yellow dots and dilated follicular infundibula containing yellowish, amorphous material, surrounded by a thin, white collaret resembling those found in chemotherapy-induced alopecia (CIA) called CIA dots [4] (Fig. 1b, c).

Three months after the end of vismodegib, the phase of regrowth started, and regrowth of a lot of circle hair and vellus hair was observed (Fig. 2a). Confocal microscopy showed shorthair in regrowth, normal in morphology with absence of dilated follicular ostia (Fig. 2b).

The second case is a 43-year-old female patient with Gorlin syndrome presented with 30 BCCs on the trunk, upper limbs, and head and neck area. The patient prac-

Fig. 2. **a** Trichoscopic evaluation shows much hair in regrowth (red circle) and few circle hairs (gray circle). **b** RCM shows shorthair in regrowth (red circle), regular in morphology with absence of dilated follicular ostia. RCM reflectance confocal microscopy.

Fig. 3. **a** Trichoscopic evaluation highlights the presence of yellow dots, broken hairs, and dilated follicular infundibula (blue circle). **b, c** RCM highlights yellow dots (yellow circle) and dilated follicular infundibula containing hair shaft remains (white asterisk) surrounded by the same necrotic-like material already described (blue arrow). RCM, reflectance confocal microscopy.

ticed since the age of 20 years several surgeries for BCC. To increase the number of lesions, we decided to start therapy with oral vismodegib (150 mg daily). The patient practiced 11 consecutive months of treatment with the disappearance of the BCCs. Currently, it is still in treatment with vismodegib alternating 2 months of treatment

to 2 months without treatment, not bringing any recurrence of the disease. The patient began to develop a grade 2 alopecia from the fifth month of treatment that developed fully at the ninth month of treatment. It has also been treated with topical corticosteroids and 5% minoxidil with hair regrowth. During the massive hair loss,

Fig. 4. **a** Trichoscopy shows several shorthairs in regrowth (red circle) and several “black and white hairs” (black arrows). **b** Highlighted shorthairs in regrowth (red circle). RCM, reflectance confocal microscopy.

trichoscopic evaluation highlighted the presence of yellow dots, broken hair, and pigtail hairs (Fig. 3a). In RCM, dilated follicular ostia with mashed, malted, nonhomogeneous material, containing normal or fragmented hair were observed (Fig. 3b, c). During the partial regrowth phase, regrowing vellus hair and several “black and white hairs” (Fig. 4a) (a sign of progressive recovery of the damaged follicular melanocytes) were observed, and RCM highlighted shorthair in regrowth (Fig. 4b).

Discussion

Vismodegib was the first Shh inhibitor approved by the US FDA on 30 January 2012 and by the European Commission on 12 July 2013 and acts by inhibiting the Shh binding selectively and inhibiting a critical signal-transducing component of the pathway, Smoothed [2]. BCC is characterized by key genetic defects in the Hh pathway, including loss-of-function mutations in PTCH1 in approximately 90% of BCC tumors and activating mutations in the G protein-coupled receptor Smoothed in 10% of BCCs [5].

Hair loss is a typical late side effect of vismodegib usage and is reversible, but regrowth takes many months. The role of the Shh pathway in hair follicle biology and epidermal homeostasis is well established. Murine studies have shown that Shh pathway inhibition in the skin can induce (reversible) alopecia and arrest of hair growth in

the telogen phase [6], which explains the occurrence of alopecia with vismodegib [7].

Vismodegib-induced alopecia is characterized by diffuse loss of hair density of the scalp. It is gradual and has a longer time to onset than that with cytotoxic chemotherapy, developing after at least 2 months [8]. According to our experience, vismodegib-induced alopecia has the same trichoscopic and RCM characteristics in both patients and resembles an AA and CIA [4]. Thanks to dermoscopy and RCM, we are also able to define the phase in which the patient is in the massive hair loss or regrowth phase [9]. Broken hairs, detected at the beginning of chemotherapy, mimic the exclamation points that are usually associated with AA and CIA. However, these are shorter than those found in AA, warning that hair damage has occurred immediately after the follicular host emergency. Pohl-Pinkus is a result of the alternation of reduction and increase in keratinocyte proliferation activity, which induces the development of constrictions and expansions along the hair shaft. This implies that the hair follicle is not usually destroyed by drug toxicity. This feature is found throughout all stages of treatment. It resembles pseudo-monilethrix in patients with AA, but in this case, the internodal tract is longer. Its pathogenesis is analogous to one of the exclamation points. However, in this instance, the damage is not severe, so to stop the mitotic follicular activity, thus after a period of decreased proliferation, it can regrow. Circle hair, pigtail, and vellus-like hair are present during prolonged chemotherapy. They are the expression of thin re-

growing anagen hair. RCM in the acute hair loss phase showed dilated follicular ostia with mashed, malted, non-homogeneous material, often containing normal or fragmented hair resembling CIA dots found in CIA. As in CIA, they may represent the earliest microscopic signs of direct toxicity of chemotherapy on hair follicle [4, 10] that persist during the whole period of chemotherapy treatment and disappear after the interruption of vismodegib.

Conclusions

Alopecia is one of the most distressing adverse events leading to vismodegib discontinuations. To our knowledge, these are the first descriptions of RCM dermoscopy in vismodegib-induced alopecia. Trichoscopy and confocal microscopy are essential to monitoring vismodegib hair loss and the response to the treatment. In order to confirm our preliminary findings, larger numbers of patients should be evaluated using these noninvasive techniques.

Statement of Ethics

Both patients signed the written informed consent for the publication of the photos and for the description of the clinical case.

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Conflict of Interest Statement

There are no conflicts of interest.

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Author Contributions

Doctors Milena Cappello, Mariateresa Cantelli, and Maria Vastarella contributed to the conception of the work, acquisition, and interpretation of data. They drafted the work, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Professor Gabriella Fabbrocini, Massimiliano Scalvenzi, and Dr. Angela Patri revised the work critically for important intellectual content; they approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final version of the manuscript.