Trichoscopy and LC-OCT findings in sonidegib-induced alopecia in patients with advanced basal cell carcinoma

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Consent for publication: the patients gave their written consent to use their personal data for the publication of this case report and any accompanying images.

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Abstract

Sonidegib is a Hedgehog pathway inhibitor (HHI) used as a first-line systemic treatment for patients with advanced basal cell carcinoma (aBCC). Alopecia is reported as a frequent adverse event (AE), occurring in 49% of patients. Forty-five patients with aBCC were treated with sonidegib between December 2022 and December 2023; among them, 11/45 patients developed alopecia. Trichoscopic features included yellow dots, black dots, exclamation mark hairs, and broken hairs. Upon LC-OCT examination, yellow dots were seen as dilated follicular dark spaces containing malted, nonhomogeneous material and outlined by bright collarets. Black dots corresponded to normal-sized follicular ostia filled with bright, homogeneous material and cadaverized hair. Exclamation mark hairs were short, dark dysmorphic hairs with different sizes of proximal and distal ends, and broken hairs were short dysmorphic hairs. LC-OCT may provide additional insights into early signs and clinical evolution of sonidegib-induced alopecia in patients with aBCC.

Introduction

Sonidegib and vismodegib are Hedgehog pathway inhibitors (HHIs) approved as first-line systemic agents for patients affected by advanced basal cell carcinoma (aBCC).[1,2] Despite the high efficacy demonstrated in clinical trials and real-life studies, the occurrence of adverse events (AEs) related to these drugs may lead to a decrease in patients' quality of life, treatment interruption, and discontinuation, with an influence on clinical outcomes. Muscle spasms, alopecia, and dysgeusia are consistently reported as the most frequent AEs during treatment with HHIs.[1,2] Alopecia is clinically characterized by diffuse hair loss and hair thinning that may extend and involve eyebrows, eyelashes, and the beard.[1,3] It develops gradually with a median time of onset of 2.9 months and is reversible after treatment cessation, even though hair regrowth takes from 6 to 12 months.[4,5] Rarely, long-lasting, persistent, or permanent hair loss can be observed.[1,3,6] Trichoscopy and reflectance confocal microscopy (RCM) have been employed to assess hair damage and severity of chemotherapy-induced alopecia (CIA), and recently, both techniques were also used to investigate patients with HHIs-induced alopecia, identifying subclinical features similar to those observed in alopecia areata and CIA.[3,7] Line-field confocal optical coherence tomography (LC-OCT) is a new imaging technique able to provide in vivo morphological assessment of skin lesions with a quasi-histological resolution.[8,9] Upgrowing literature data supports its valuable role in the non-invasive diagnosis of skin cancers and inflammatory skin conditions, and preliminary findings have also been reported for hair loss in different diseases of the scalp.[10-13] The acquisition depth

permits a global evaluation of the hair infundibula with pathological changes at different levels, up to mid-dermis. This study describes clinical, dermoscopic, and LC-OCT findings of sonidegib-induced alopecia in patients with aBCC.

Case Report

The CE-marked DeepLive LC-OCT device (DAMAE Medical®, Paris, France) was used to perform this study. The entire system consists of a portable probe connected to a central unit and a display. It provides high-definition videos/images (axial resolution ≅1.2 µm, lateral resolution ≅1.3 µm) up to superficial/mid dermis (≅500 µm) within a field of view of 1.2 mm. 3D cubes/slices are also quickly generated thanks to dedicated software. On the screen, the image is visualized together with the corresponding dermoscopic image, indicating the position of the probe tip during the exam. Clinical and video-dermoscopic images (Dermalview Dual, Gavimedica srl, Camposano, Italy), and LC-OCT videos/images were recorded for each lesion, and at least one high-quality vertical LC-OCT video and three horizontal LC-OCT videos/images at various depths (epidermis, dermal-epidermal junction, and superficial dermis) were considered pertinent for the evaluation. When available, a 3D cube was included in the image analysis. LC-OCT features were evaluated according to established RCM criteria (for horizontal sections), and LC-OCT described criteria (for vertical sections).[3,7,12,13] Statistical analysis was performed as absolute frequencies, and their percentages were calculated for qualitative variables.

This study was performed at the outpatient clinic of the Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy. The dedicated database was examined, and patients with aBCC who underwent LC-OCT examination from December 2022 to December 2023 for sonidegib-induced alopecia were included in the study. Clinical and demographic variables were gathered for each patient. The severity of alopecia clinical presentation was assessed according to the 5-point grading scale introduced in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[14]

Of the 45 patients treated with sonidegib in our unit (24 females and 21 males), with a mean age of 77 (27-96 years), 11 patients (8 females and 3 males), with a mean age of 69 (27-90 years), developed various grades of alopecia (Table 1).

The onset of alopecia with initial hair loss occurred after a mean time of 3 months (2-8 months), while a higher severity of hair loss occurred after a mean time of 6 months (3-12 months). Eight of the 11 patients developed grade 1 alopecia (<50% of the entire scalp), and 3 patients had grade 2 alopecia (>50% of the entire scalp) (Figure 1a), based on the CTCAE grading scale. Trichoscopic features included: i) yellow dots (9/11 patients), ii) black dots (9/11), iii) exclamation mark hairs (8/11), and iv) broken hairs (4/11) (Figure 1 b,c).

Yellow dots were seen in vertical and horizontal LC-OCT as dilated follicular dark spaces containing malted, slightly bright, non-homogeneous material outlined by brighter collarets with perifollicular inflammatory cells; no terminal or vellus hair shafts were recognized within the infundibula (Figure 1 d,e). Assessment of black dots by LC-OCT showed normal-sized follicular ostia collecting bright, homogeneous material and cadaverized hair. The main LC-OCT findings of exclamation mark hairs were the presence of short dark dysmorphic hairs with different sizes of proximal and distal ends, while broken hairs corresponded to short dysmorphic hairs (Figure 1 d,e). 3D image reconstruction showed the collection of bright amorphous material along the entire length of the infundibula, both in yellow dots and black dots (Figure 1e).

Discussion

HHIs are a relatively new class of therapeutic agents that act by targeting the proteins involved in the regulation of the Hedgehog pathway.[1,2,6] It is well recognized that, in humans, Hedgehog signaling is an essential key player for the proliferation of the hair follicle epithelium and for the modulation of the hair cycle.[5,15] In our study, 24% of the patients with aBCC developed alopecia during treatment with sonidegib. The onset of alopecia occurred after a mean time of 3 months of treatment, with a severe hair loss stage occurring after a mean time of 6 months. Previous studies reported alopecia occurring in up to 49% of the cases, with a median time to onset of 5.5 months.[16,17] HHIs-induced alopecia is thus considered a class-related effect, with a molecular mechanism that is supposed to prevent hair follicle transitioning from the anagen phase to the telogen phase.[5,15] Hair loss represents a type of telogen effluvium caused by the interference of HHIs with the hair cycle, with a biological effect that differs from damage to hair-matrix keratinocytes commonly occurring in conventional chemotherapy-induced alopecia (CIA) that induces anagen effluvium.[7,18] However, in our experience, we often found clinical and

Table 1. Patient demographics and clinical data.

Patient	Age	Sex	BCC localization	Initial hair loss*	Severe hair loss*	Grade**
1	27	F	Trunk	4	6	I
2	58	M	Zygomatic area	2	4	I
3	59	M	Trunk	3	5	II
4	72	F	Lower eyelid	5	8	I
5	73	M	Preauricular area	8	12	I
6	75	F	Lower eyelid	4	7	I
7	77	F	Retroauricular area	2	3	I
8	77	F	Leg	3	4	II
9	82	F	Medial canthus	8	12	I
10	85	M	Trunk	2	3	II
11	90	F	Lower eyelid	4	8	I

F, female; M, male; BCC, basal cell carcinoma; *months after starting therapy; **according to Common Terminology Criteria for Adverse Events version 4.0.

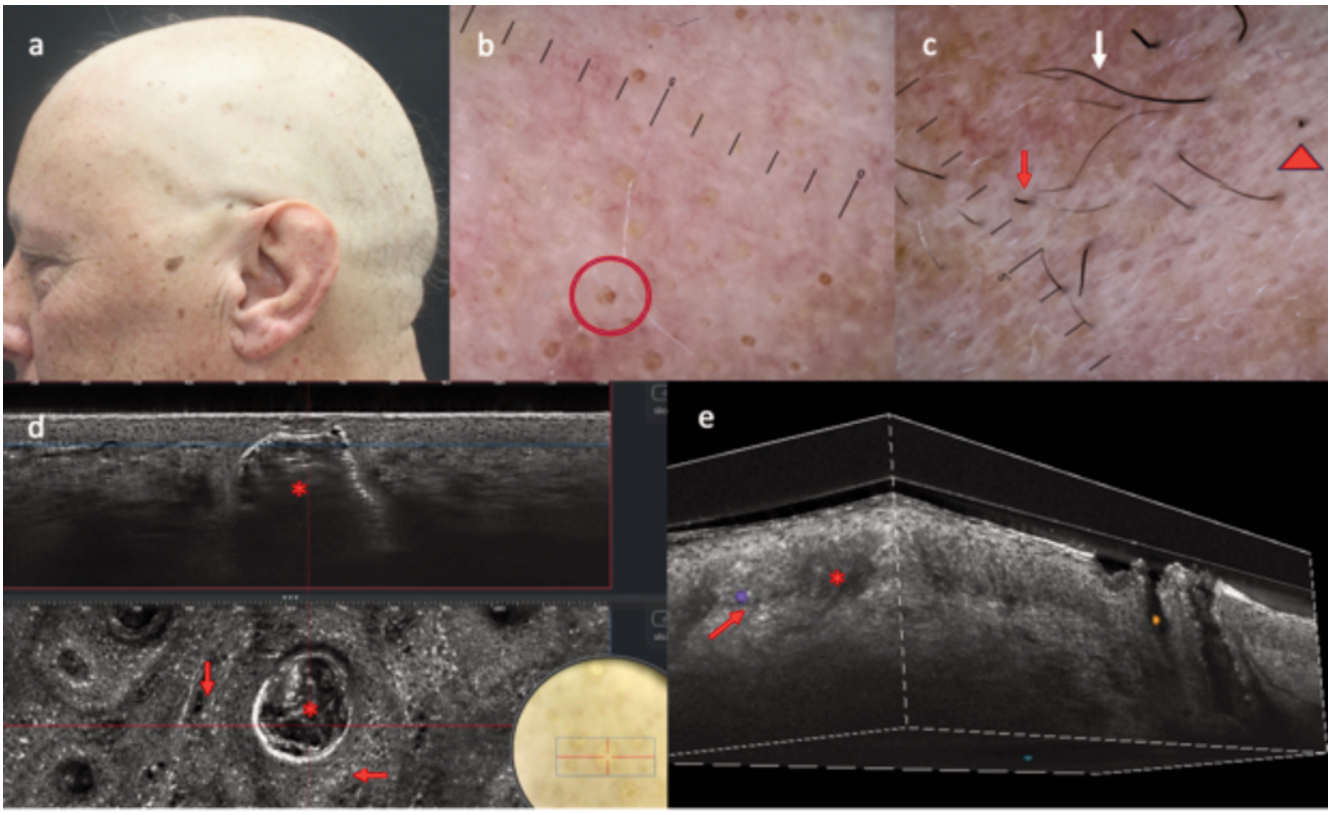

Figure 1. Clinical, dermoscopy, and LC-OCT findings of sonidegib-induced alopecia in a 76-year-old man. **a**) Diffuse alopecia with **b**) dermoscopic features of yellow dots (red circle) and **c**) dermoscopic features of black dots (red arrowhead), exclamation mark hairs (white arrow) and broken hairs (red arrow); **d**) vertical and horizontal LC-OCT section showing the amorphous material within the yellow dot (red asterisks) with peri-follicular bright inflammatory cells (red arrows), as also seen in **e**) 3D mode.

dermoscopic findings commonly described in alopecia areata. Indeed, yellow dots and black dots are considered characteristic markers of alopecia areata, even though they are observed in various hair diseases.[3,7,19]

By LC-OCT we detected the main findings of the acute hair loss phase: yellow dots were seen as dilated follicular ostia with luminal structure fulfilled by bright amorphous material corresponding to keratin and debris, and vertical and 3D sections highlighted the involvement of the entire infundibula along with deep-seated peri-adnexal inflammatory clusters; black dots showed ill-defined grayish material, with a normal dimension of the lumen containing cadaverized hairs; exclamation mark hairs and broken hairs were characterized by morphologic alterations of the hair shaft that delineated an atypical diameter of the structure. Combining trichoscopy and RCM has enabled the characterization of different phases of the disease in CIA and HHIs-related alopecia (initial hair loss, massive hair loss, partial regrowth, total regrowth), as different morphological criteria were related to a specific disease phase, using these non-invasive techniques.[3,20] Additionally, trichoscopy and RCM have been demonstrated to be valuable tools in monitoring treatment response and clinical remission in different scalp diseases.[3,19,20] Future studies employing LC-OCT at different time points may identify subclinical findings associated with the active or remission phase of HHIs-related alopecia and other diseases of the scalp. The main limitations of this study included the retrospective design and the inclusion of a small sample size, the latter probably related to the low incidence of this entity in clinical settings.

Conclusions

In conclusion, since alopecia represents one of the most distressing AEs leading to therapy interruption and discontinuation in patients with aBCC,[4,5] digital LC-OCT may add further insights on the disease stage and severity, revealing in vivo subclinical alterations that involve follicular ostia and thus representing a complementary exam to clinical-dermoscopic evaluation.

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