Dermatology Practical & Conceptual

Line-Field Optical Coherence Tomography: Usefulness in the Non-Invasive Differential Diagnosis of Congenital Alopecia of Infancy

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ABSTRACT

Introduction: Soon after birth, the clinical differential diagnosis between sebaceous of Jadassohn (NSJ), congenital triangular alopecia (CTA) and aplasia cutis congenita (ACC) may be challenging. A certain overlap of standard dermoscopic features can occur, especially in atypical cases, depending on scalp skin morphology and maturation age. The recently developed line-field confocal optical coherence tomography (LC-OCT) can provide morphological skin details with cellular resolution trough a rapid non-invasive examination.

Objectives: To assess the LC-OCT features of 6 cases of congenital alopecia of different aetiologies, with both typical and atypical clinical appearance.

Methods: A non-invasive imaging examination combining standard dermoscopy, high-resolution videodermoscopy (HRVD) and LC-OCT was realized in 7 babies presenting for congenital alopecia with overlapping features, aged between 5 months and 5 years.

Results: Based on the specific LC-OCT features, and supported by HRVD features, a diagnosis of NSJ, congenital triangular alopecia (CTA) and AC) were made in 4, 2 and 1 case, respectively.

Conclusions: The combined LC-OCT plus HRVD non-invasive imaging bring the advantage to have a real time diagnosis, to set the proper management and allows to avoid a skin biopsy in the perinatal age/first years of life at delicate skin site.

Introduction

The field of congenital alopecia counts within it several differential diagnoses [1-6]: among them, the most commonly observed cases are due to nevus sebaceous of Jadassohn (NSJ) [1], congenital triangular alopecia (CTA) [2] or aplasia cutis congenita (ACC) [3]. Dermoscopic examination at standard resolution (17-20X enlargement) proved to help dermatologists and pediatricians in orienting the correct diagnosis and therapeutic approach in most cases [7-8]. However, the clinical manifestation of these three conditions may be similar during the first years of life, as the pathognomonic features of the various lesions are not yet fully defined [4-6]. Recently, new non-invasive imaging tools providing high-definition images have been released, including high resolution videodermoscopy (HRVD) [10] and line-field confocal optical coherence tomography (LC-OCT) [11] which are particularly helpful in difficult cases with overlapping features and provide further details compared to standard dermoscopy [5-7,10-11,14-17].

HRVD allows to visualize the skin and mucosa, in polarized-light mode (wave-length λ=380÷700 nm), ranging from 30 to 400-fold enlargement. Thanks to its versatility and non-invasive application, it was employed since today for both the diagnosis and follow-up of children disorders affecting hair [12] and vascular structures [13].

LC-OCT is a recently developed device that combines the technology of conventional OCT and the cellular resolution of reflectance confocal microscopy, able to explore the skin both vertically and horizontally: it allows a penetration up to ~400 µm (ie m/deep dermis, according to the anatomic site) and an isotropic resolution of ~1 µm. Briefly, LC-OCT is an echo-based imaging modality that measures the time of flight and amplitude of light a (.e supercontinuum laser emitting at 400 nm) backscattered from the sample microstructures. It is based on the principle of OCT, with spatial filtering characteristic of RCM incorporated through line illumination and detection. The main advantage relies of the fact that, *in vivo*, the imaging mode can be switched from vertical to horizontal and vice versa. Among the various field of application in dermatologic diagnostics, the LC-OCT provided a nearly "virtual histology" in childhood inflammatory [14,15], infectious [15,16], vascular [17] and tricologic [18] disorders.

To date, there are no reports on the LC-OCT examination of pediatric alopecia, while it has been successfully used in adults to monitor the efficacy of alopecia areata treatment [19].

Objectives

We here aimed to describe, for the first time, the findings obtained through the non-invasive examination of congenital alopecic patches with equivocal clino-dermoscopic appearance.

Methods

Between October 2019 and May 2023, seven pediatric patients were referred for consultation in the pediatrics dermatology service of the Dermatologic Unit in Siena University Hospital: all of them had a single alopecic patch of the frontal/parietal/vertex area, with unclear clinical appearance. Each patients was imaged with clinical pictures, HRVD and LC-OCT.

High Resolution Videodermoscopy

HRVD was realized with *HS600 Horus* (Adamo S.r.l.) both in contact (from 30X [Figures 1B, Figures 2, B and F, Figure 3B] to 100X [Figures 1 C and G, Figures 2, C and G, Figure 3C magnification) and non-contact. Non-contact HRVD images (Figure 1F) were taken were by applying a customized adapter between the skin and the probe (field of view – FOV- of 15 mm, ~15x.

Line-field Confocal Optical Coherence Tomography

LC-OCT was performed with *Deeplive*® (Damae). The device is equipped with a polarized light dermatoscope with a field of view of 2.5 mm and a resolution of 5µm that allows manual localization of the LC-OCT probe inside the dermoscopic image. During skin examination, on the device display, a dermoscopic frame is visualized along with the LC-OCT image: the red line indicates where the probe tip is placed within the lesion and corresponds to the field of view on a vertical plane of the LC-OCT laser -1.2 mm examination field- (Figures 1, D and H, Figure 2D, Figures 3, D and H). For each patient, sequential multiple LC-OCT examination including 2D (vertical and horizontal) and videos were performed at presentation time over the lesions at 3 main points (ie center of the lesion, lesion margin, perilesional skin – ie 1.5 cm from the lesion margin; examination on healthy skin was also performed, as a control. If necessary, a 6-mm self-adhesive paper reinforcement ring was used to ensure the correct position of the probe before imaging. A drop of paraffin oil was applied to the tip of the handheld probe before application to the skin, as previously described [11,20]. Each examination was performed by applying minimal to no pressure on the skin in order to ensure a correct visualization of the stratum corneum. Then, using a specific software (MinIP, 3DSlicer, version 4.10.2), it was possible to obtain 3D image (1.2 x 0.5 x 0.5 mm) of the lesions from each video as previously described [21]. Briefly, the software elaboration also allows to virtually navigate inside the rectangle following the 3 axes, to measure stain-specific cells/structures.

Results

Patients were aged between 5 months and 3-years, with an average age of 1.6 years. Four children had NSJ of the vertex, parietal and fronto-parietal area, one had ACC of the vertex and two had CTA of the frontal or parietal area. Lesion maximum diameter ranged from 2.1 to 4.8 cm, with average value of 3.6 cm. Specific LC-OCT findings of each condition are described below, along with clinical, dermoscopic features and pathological correlates.

Nevus Sebaceous of Jadassohn

A total of 4 patients were diagnosed with NSJ: lesions were undergoing different evolution phases, giving reason to the different clinical and dermoscopic appearance. In tree patients, aged 2 (Figure 1A), 0.8 (Figure 1E) and 1.2 years (Figure 1H) respectively, we observed a second-phase (papillomatous) NSJ localized on the temporal (Figure 1A), parietal (Figure 1E) and vertex (Figure 1H) area, respectively. Patchy alopecia was present due to the presence of skin-colored o slightly erythematous-yellowish plaques, ranging from elongated to roundish in shape, and verrucous surface. Under HRVD, multiple yellowish globules were visible over an orangish /pinkish background, along with bright white keratin dots delimited by evident vessels arranged in a meshed pattern (Figures 1, B,C,F and I). These structures corresponded to hyperplastic aggregated sebaceous glands, keratin plugs at follicular hostia and papillary vessels, respectively. LC-OCT vertical imaging (Figures 1, D, G and L) revealed normal epidermal layers, hyperreflective triangular structures (triangle) -corresponding to keratin plugs at the hostium of empty follicles (arrows); near to the hair follicle, hypo-reflective lobular structures circumscribed by a rim of hyperreflective roundish cells (asterisk) corresponded to sebaceous glans. Thickened papillary dermal branches were visible as hyperreflective linear structures (arrowheads) and dilated papillary vessels as hyporeflective round holes (v). Then, we diagnosed a 3-year-old boy with a NSJ with atypical appearance, previously misdiagnosed as ACC due to the depressed surface and prolonged duration of the first-phase (atrophic) in the first 2 years. However, the parents noticed the appearance of multiple soft wart-like elements and small crusts in the last year; occasional bleeding was also referred. Physical examination revealed an irregular-shaped slightly depressed skin area of the vertex: lesional surface appeared erythematous to skin-colored and covered by multiple thick whitish to yellowish scales and tiny digitiform yellowish/brownish wart-like structures (Figure 2E). HRVD revealed dilated in focus vessels, yellowish dots not associated with hair follicles and digitiform structures in which each protrusion hosted a linearly disposed capillary (Figures 2, F and G); sparse vellus hairs were also visible as bright white linear structures. LC-OCT showed: normal epidermis, hypertrophic sebaceous glands not associated with hair follicle, thick dermal branches delimiting lobular structures, dilated capillary vessels and sporadic immature hair follicle (Figure 1H). Based on these findings, we leaned towards a diagnosis of NSJ in early phase with atypical presentation (the stage was unusual given the patient age) and ruled out the presence of warts. All patients were both scheduled periodic follow-up visits (every 9 months).

Aplasia Cutis Congenita

A 5-month-old baby came to our attention to evaluate an erythematous oval alopecic patch in the parietal area of 3.3 x 2.5cm (Figure 2A), previously diagnosed as NSJ. Clinically, margins were well-demarcated and the surface lightly depressed. HRVD highlighted multiple yellowish dots and globular structures, in focus thick vessels, some white/yellowish thick scales; no vellus hairs, hairs root nor bulbs arranged along the lesion margins (Figures 2, B and C). LC-OCT imaging revealed the atrophy of the skin, with thinned epidermal layer, slight hyperkeratosis and absence of adnexal structures; moreover, a dense papillary dermis (due to reduction in elastic fibers and increase in collagen fibers) was visible due to hyper-reflective horizontal strands and elongated are flective spaces corresponding to compressed papillary vessels, as in scar-like tissues (Figure 2D). Based on clinical and imaging findings, a diagnosis of a ACC membranous type was made: parents were recommended avoiding sun exposure and attend regular follow-up.

Congenital Triangular Alopecia

A 1-year-old baby was referred to investigate an oval-shaped alopecic patch of 4x2cm localized between the frontal and vertex area of the scalp (Figure 3A), aver having received a diagnosis of ACC. The skin was clinically unaltered; HRVD showed a slightly erythema in the center and normal skin-color at the periphery, multiple short vellus hairs and yellowish dots corresponding to empy follicular openings filled with keratin (Figures 3, B and C). LC-OCT revealed normally developed skin layers and sebaceous glands, slightly dilated capillary vessels, normal collagen and some immature hair follicle bulge (Figure 3D). Based on these findings, a diagnosis of CTA was posed. Indeed, identical findings were observed in a CTA case with typical triangular shape and location at the temporal area (Figure 3D) in a 3-year-old girl. Here, some terminal hairs along with long vellus hairs were detected by HRVD (Figure 3, F and G), while the LC-OCT revealed normal epidermis, dermis and adnexa, with the exception of a focal slight infundibular hyperkeratosis (Figure 3H). No follow-up was planned for both patients.

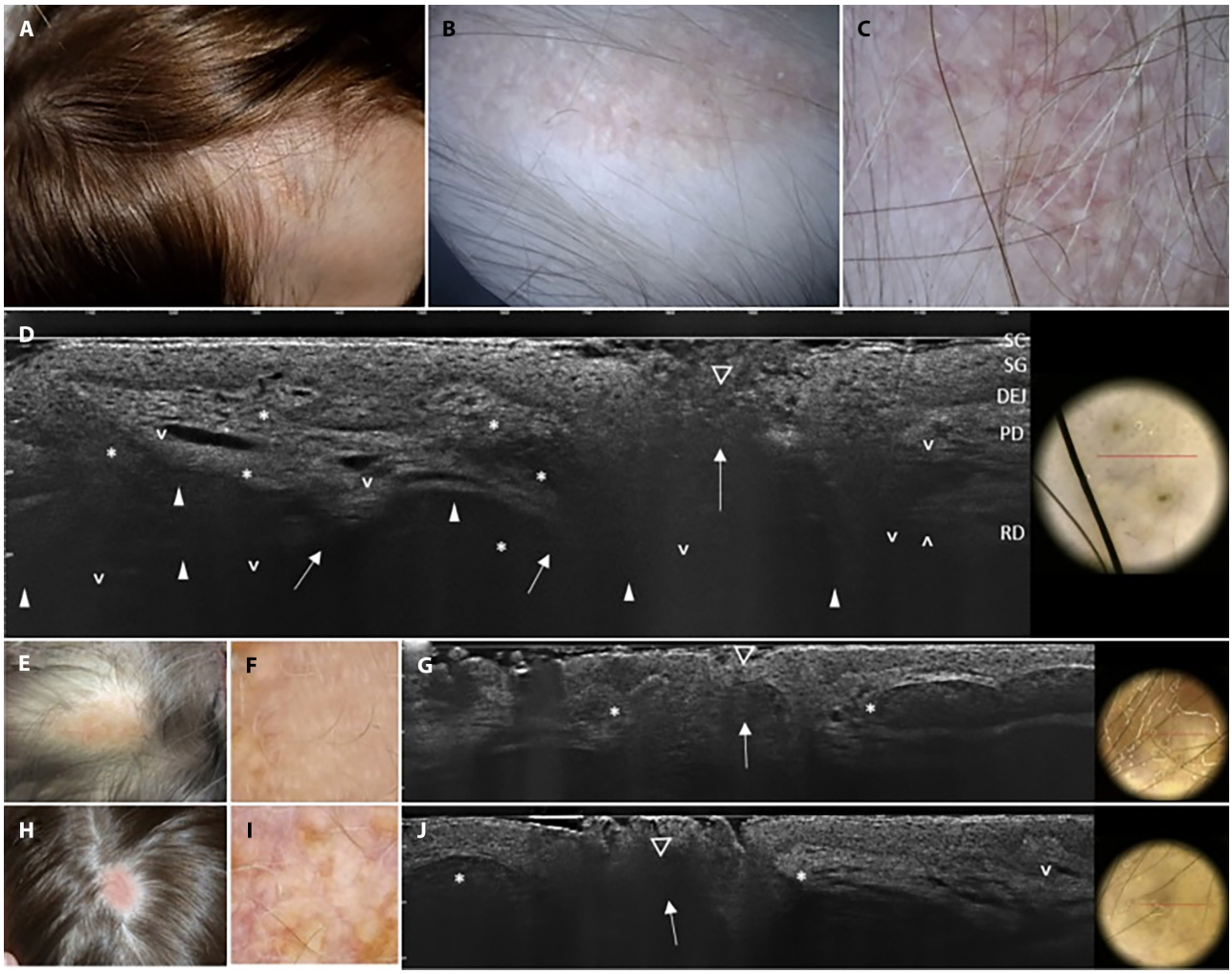

Figure 1. Nevus sebaceous of Jadassohn of temporal (A), parietal (E) and vertex (H) area, in a 2-years-old girl (A) and boys aged 0.8 (E) and 1.2 years (H). Clinically, patchy alopecic areas due to the presence of a rough plaques either skin-coloured (A) or erythemato-yellowish (E,H) characterized by cobblestone to verrucous surfaces. Polarized dermoscopy 20X reveals a brilliant white dots corresponding to keratin plugs in a yellowish-reddish background (B,F,I) while high-resolution dermoscopy reveals linear capillary vessels separating yellowish roundish areas corresponding to sebaceus glands coalesced to lobular structures (C, 100X). Under vertical LC-OCT imaging at lesional site (red line inside the dermoscopic frame, D,G,I), multiple sebaceous glans (asterisk) (ie hypo-reflective tightly packed roundish cells, focally aggregated in lobules surrounded by an hyperreflective rim) appear to be connected to the hair follicle (arrow) and delimited by hyper-reflective thick dermal branches (arrowheads). Keratin plug (triangle) is also visible at follicular openings, where no hairs are present. Capillary vessels appear as are flective roundish or elongated structures (v).

SC = stratum corneum; SG = stratum granulosum; DEJ = dermal-epidermal junction; PD = papillary dermis; RD = reticular dermis; v = vessels.

Conclusions

Soon after birth, the clinical differential diagnosis between NSJ in its early stage with atrophic appearance and ACC may be difficult [5,6]. Although rarely, CTA cases can be localized outside the typical temporal area and have an ovalar rather than a triangular shape, or can show erythematous skin, leading to misdiagnose with NJS or ACC [9,22-26].

Also known as "pilosyringosebaceous nevus", NSJ is a rare congenital hamartoma that mainly occurs on the face or scalp [1]. The lesion evolves typically through the years: at the first stage exhibits a smooth velvety surface, a partially or complete alopecia and yellowish pink/yellowish-orange colour, characterized by a paucity of underdeveloped sebaceous glands and hair follicles. At the second stage NSJ tends to become raised and verrucous with mild hyperkeratosis and acanthosis, intense sinuosity of the dermo-epidermal junction and developed sebaceous glands [1-7]; then, in response to androgen, sebaceous glands become hyperplastic and hair can occur; finally, during adulthood, the development of secondary neoplasms can be observed, predominantly but not exclusively benign [22-24].

ACC of the scalp (membranous or non- membranous) or is a focal or diffused skin defect that mostly affects epidermis and dermis, although subcutaneous tissue, bone and

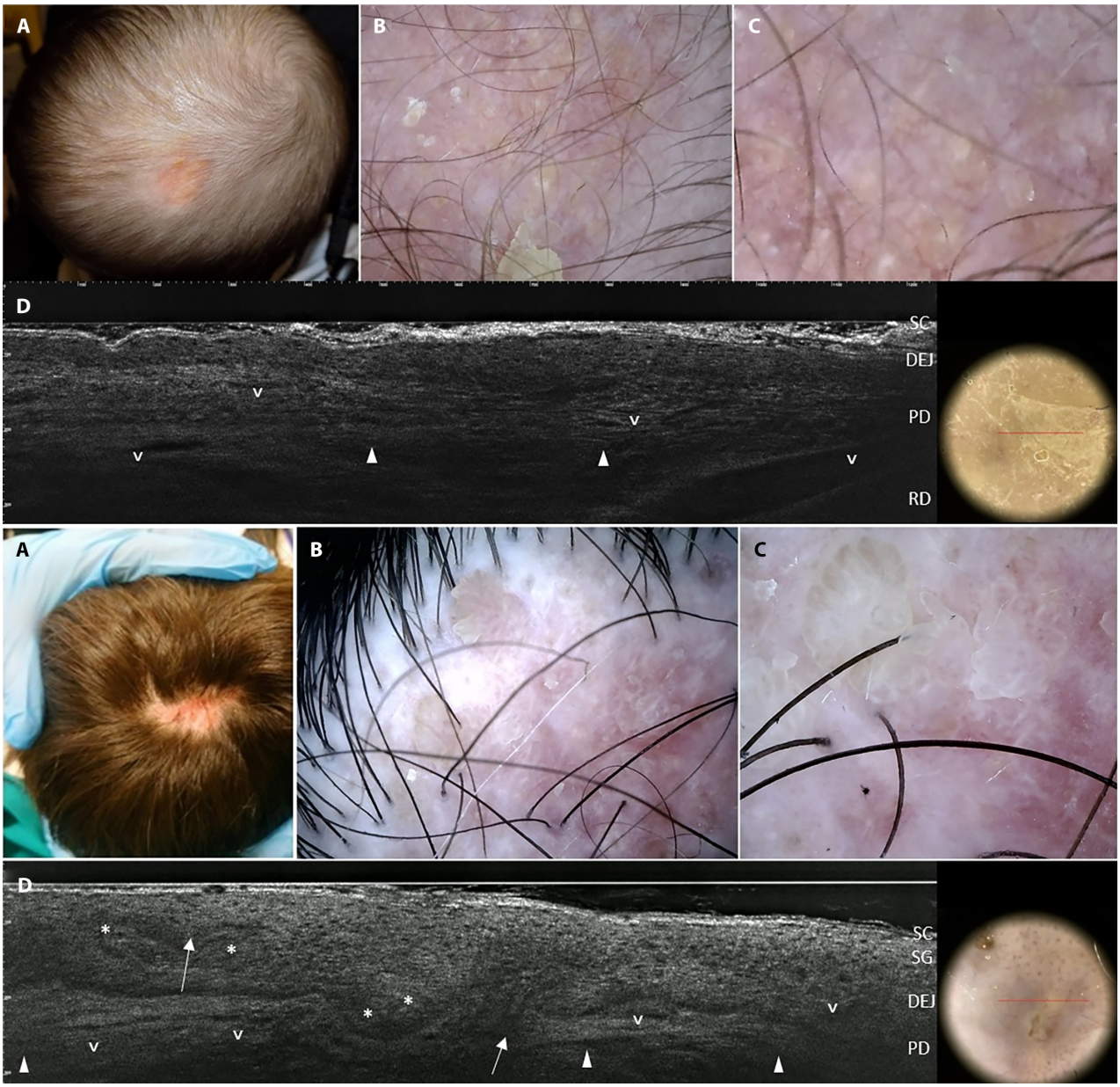

Figure 2. Aplasia cutis of the parieto-temporal area in a 5-months old boy. Polarized dermoscopy 30x (B) and 100x (C) highlights the presence of yellowish hyperkeratostic plugs and well-visible papillary vessels due to skin atrophy. LC-OCT (D) detect a bright hyperreflective dense stratum corneum in correspondence of an hyperkeratosic scale (right part of the LC-OCT frame/red bar) and a thinned stratum corneum in the left part right of the LC-OCT frame/red bar (H). The epidermis is thinned, and single layer are not detectable, while the dermal-epidermal junction is well-visible. Are flective elongated areas correspond to linearly disposed capillary vessels (v) while hyperreflective branches correspond dense dermal collagen (arrows). Differential diagnosis with an atypical NSJ of the vertex presenting as a depressed erythematous patch in a 2.4-years-old boy (H). Multiple yellowish plugs and digitiform protrusions, with linearly arranged capillaries under high resolution dermoscopy (F, 30X;G, 50X). LC-OCT (H) reveals multiple sebaceous glans (asterisk) connected to empty hair follicle (arrow), dilated vessels in the dermal papillae (v) and collagen bundles (arrowheads).

meninges can also be involved. The size of the lesion can be variable, with a smooth and atrophic surface, occasionally covered by a translucent membrane or erosion [9,25]. Under standard dermoscopy, ACC of the scalp resembles deep-reaching scars, with lack of hair follicles and a translucent appearance [5,9].

CTA is also known as "temporal triangular alopecia" due to this peculiar localization: it consists of a benign non-cicatricial pattern of hair loss which can manifest at birth or develop in the first years of life of unknown etiology, in which miniaturization of hair follicles is followed by vellus hair growth [26]. Trichoscopy shows a normal total number of miniaturized hair follicle units with long thin vellus

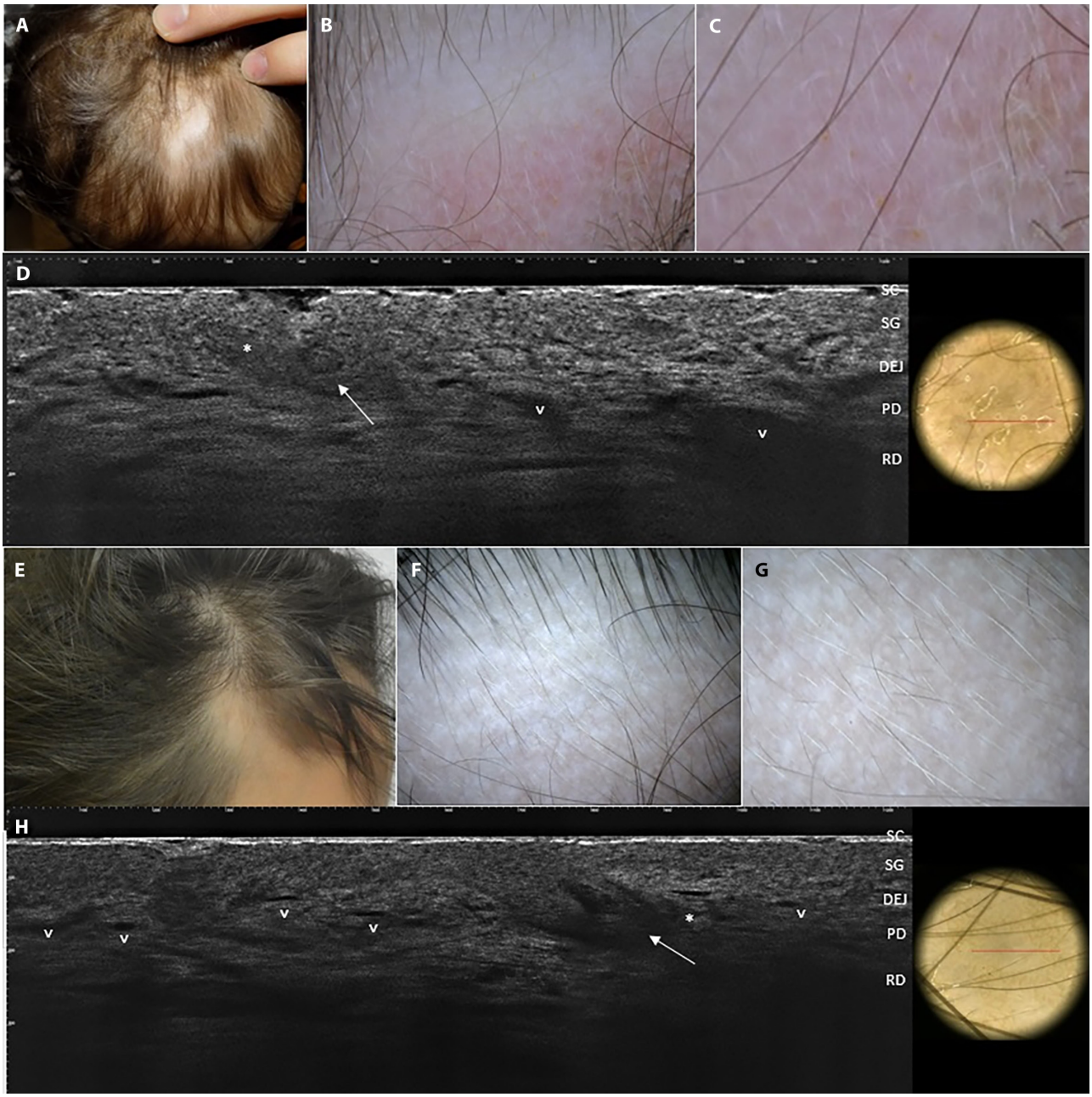

Figure 3. Triangular congenital alopecia in two girls aged 1.5 (A) and 3 (E) years. In the lesion localized at vertex-frontal area, HRVD reveals the presence of vellus hairs, sporadic terminal hairs, yellowish dots and slight central erythematous background in case 1 (B,C); LC-OCT vertical imaging (D,H) demonstrates normal epidermis, normal sebaceous glans (asterisks), dilated capillary vessels (v) and small skin hair follicle bulges (arrows) in both cases. The lesion of the frontal-temporal area (E), HRVD shows both multiple vellus hairs and few terminal hairs (D) and empty follicular openings (G, circles), while LC-OCT detects a normal epidermis, capillary vascularization (v) and sebaceous glands (asterisk) (H), with normal hair bulges in vertical sections (arrows) corresponding to vellus hairs; slight infundibular hyperkeratosis at hair bulge (arrow). Collagen fibers shows normal density in both cases (D,H).
SC = stratum corneum; SG = stratum granulosum; DEJ = dermal-epidermal junction; PD = papillary dermis; RD = reticular dermis; v = vessels.

hairs surrounded by normal terminal hairs in the adjacent scalp [2,4,8,27]. Standard dermoscopy can often orient the diagnostic suspect revealing the presence of vellus hair/lack of hair follicles or define a given capillary vessels pattern [5,6]. However, a certain overlap of dermoscopic features can occur, especially in atypical cases, depending on scalp skin morphology and maturation age: indeed, multiple thick yellowish scales, few globular yellow-whitish dots and in focused vessels with meshed arrangements can be visible in both NSJ and ACC cases; vellus hairs and yellow dots are visible both in NSJ and CTA.

Here in these cases, the LC-OCT examination allowed to reach a definite diagnosis by providing an alternative to the histopathologic examination through the *in vivo* virtual histology with cellular resolution. Indeed, LC-OCT imaging detected the main alterations of the epidermal and upper dermal layers and adnexa structures, such as: dimension/number/hyperkeratinization of the hair follicle bulge, number/dimension of sebaceous glands, atrophy/alteration of the epidermis, presence of empty hair follicle filled with keratin or vellus hair. All LC-OCT findings obtained with clinically atypical NSJ and CTA cases (Figures 2, E-H and Figures 3 A-D) were compared with those obtained in clear-cut NSJ, ACC and CTA cases (Figures 1 and 3, Figures 3 E-H). Correlation of LC-OC findings and HRVD features was also performed.

In conclusion, the early differential diagnosis of patchy alopecia of the scalp is of main importance in order to set up appropriate management, which vary widely according to each specific case. Long/occasional follow-up is performed in CTA, due to the benign course. Close follow-up visits in children with NSJ allow early diagnosis of possible malignant evolution of the lesion and screening of Linear nevus sebaceous syndrome [22,24]. Then, MRI of the head should be performed in case of midline membranous/bullous scalp to rule out the presence of ectopic neural tissue, while ultrasound is suggested to exclude underlying bony defects in large lesions; in case of non-membranous ACC of the scalp, limb defects should be searched to rule out Adams-Oliver syndrome, then close follow-up visits to manage the healing/if surgically treatment of the defect is needed [28].

The combined HRVD and LC-OCT non-invasive imaging bring the undoubtful advantage to have a real time diagnosis and avoid a skin biopsy in the perinatal age/first years of life at delicate skin site.

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