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RESEARCH ARTICLE

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Hidradenitis suppurativa: Morphologic and vascular study of nodular inflammatory lesions by means of optical coherence tomography

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Abstract

Hidradenitis suppurativa (HS) is an inflammatory disease characterized by a recurrent-remission trend and clinical lesions that range from asymptomatic to inflamed, deep-seated nodules with scarring and suppuration. The aim of our study was to identify morphologic and vascular features of HS nodules by means of dynamic optical coherence tomography (D-OCT) and to define if they are correlated to patient endotype and risk of disease progression. A set of standardized clinical pictures and D-OCT images were acquired from 57 inflammatory nodules of 40 patients affected by HS. A set of 20 clinical and D-OCT images were acquired from 20 healthy volunteers as a control group. The comparison of D-OCT features among HS and control group was analysed. The correlation between HS patient endotype and D-OCT features of the lesions was calculated. D-OCT enabled to identify vascular and morphological aspects characterizing HS nodular inflammatory lesions. In addition, several D-OCT features were significantly different among distinct disease endotypes. The characterization of HS nodular inflammatory lesions through D-OCT, corresponding to blood vessel dilation and inflammatory associated hyper-vascularization, may have important clinical consequences in the assessment of HS risk of progression, therapeutic decisions and treatment efficacy monitoring.

KEYWORDS
endotypes, Hidradenitis suppurativa, optical coherence tomography, therapy, vascularization

1 | INTRODUCTION

Hidradenitis suppurativa (HS) is a relapsing-remitting inflammatory disease characterized by a progression of asymptomatic nodules to deep-seated lesions and fistula formation that leads to suppuration and scarring, with functional limitation and aesthetic disadvantage.[1,2] The aetiology of HS is multifactorial and involves both genetic and environmental factors. The pathogenesis includes the following: follicular occlusion, altered immunological response and bacterial colonization; moreover, hormones, obesity and smoking contribute to disease worsening.[3–5]

Current pathogenic models showed that HS starts around the hair follicle, indeed the first reported events are infundibular acanthosis, hyperkeratosis and local immune cell infiltration.[6,7] The

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infundibular changes induce follicular occlusion and a phlogistic reaction with eventual rupture of the epithelial capsule and bacterial proliferation.[6–9] These anatomic and inflammatory events lead to the formation of clinically visible dermal nodules and abscesses which may evolve into pus-draining epithelialized sinus tracts, fistulas and eventually to fibrotic scarring.[7–10]

HS diagnosis is clinical and relies on the presence of the following signs: typical lesions such as nodules, abscesses, tunnels and scars; localization mainly at the axillae and groin; and a relapsing-remittent disease course.[11,12] Considerable variability occurs in the clinical presentation, disease severity and treatment response, with a broad spectrum of possible HS presentations and comorbidities.[8,13–15] Regarding possible risk factor for HS progression, several studies identified male sex, being overweight or obese, smoking, a long-term history of the disease and the presence of lesions in the perianal, axillary and inframammary area as important prognostic elements.[16,17]

Several phenotype classifications have been proposed, based mainly upon the clinical distribution of lesions and the lesion types (i.e. comedones, nodules and presence of scarring or tunnels).[8,18] Recently, Martorell and colleagues identified three HS endotypes: the follicular (FP), the inflammatory (IP) and the mixed phenotype (MP).[19] The FP is characterized by the presence of folliculitis with multiple comedones and phlogistic nodules that are not coalescing. On the contrary, IP is characterized by the presence of abscesses and thick fistular tracts that tends to coalesce into poorly defined inflammatory plaques, in the absence of folliculitis or comedones. The authors observed that these endotypes are associated with distinct clinical courses, in fact, while FP patients present an indolent disease, IP-affected individuals often show a rapidly progressing course characterized by the formation of complex coalescent lesions over a short period of time.[19] Intriguingly the presence of IP disease was associated with increased cardiovascular risk, probably because of the presence of higher local and systemic inflammatory phenomena.[20]

Dynamic optical coherence tomography (D-OCT) is a novel non-invasive imaging technique based on the physical principle of low coherence interferometry that has been used for the diagnosis and characterization of skin cancers and inflammatory diseases.[21–23] It offers a fast and reliable evaluation of the epidermis and dermis up to 1 mm of depth, as well as the microvascular changes in blood flow, allowing an accurate morphological and a functional characterization of skin lesions. Indeed, en vivo blood flow can be visualized by means of cross-sectional images. Recently, we described the morphologic and functional features of comedos, papules and pustules in acne, analysing their characteristics and describing their evolution from their genesis to their resolution, with non-invasive imaging devices.[24,25] To our best knowledge, D-OCT features of HS nodules have not yet been described.

The aim of our study was to assess and describe D-OCT morphological features of nodular inflammatory HS lesions and to determine if different D-OCT features were associated with a distinct phenotype of the disease.

2 | MATERIALS AND METHODS

A retrospective case-control study of HS patients and age- and sex-matched control cohort was carried out at the Dermatology Department of the University of Modena and Reggio Emilia between January 2018 and June 2021. HS patients were selected based on active consent for both clinical and D-OCT image acquisition with mild-moderate disease, determined according to the HS-Physician Global Assessment (PGA) severity scale[26] and the presence of at least 1 inflammatory HS nodule. Patients under any HS specific therapy during the 4 weeks before image acquisition were excluded. HS patients were furtherly classified into one of the endotypes previously described by Martorell et al.[19] D-OCT images were acquired from nodular inflammatory lesions that were selected according to clinical characteristics. Epidemiologic and clinical data were recorded in a dedicated database and analysed.

Standardized clinical pictures were acquired through the Canon G16® (Canon Inc., Canon Park, Melville, NY 11747, USA) and the Canfield Close-up Scale® (Canfield Imaging Systems, Fairfield, NJ, USA). D-OCT images were acquired with the VivoSight® D-OCT (Michelson Diagnostics Ltd, Eclipse House, Sittingbourne Road, Maidstone, Kent, UK). Vertical and horizontal-plane OCT images, along with functional data (blood flow information) are immediately displayed on the structural OCT images as an overlay, so that the relationship between the vessels and the structural images can be visualized in real time. Areas of motion are coloured red. A "stack" of 120 D-OCT images was captured for each lesion to form a 3-dimensional (3D) "data block." D-OCT images were processed using an automatic software protocol and 3D image reconstruction software.[27]

The control group included 20 age- and sex-matched volunteers, who consented to healthy skin D-OCT image acquisition of the axillary or groin regions.

The study was performed in conformity with the ethical guidelines of the Declaration of Helsinki and in compliance with the ethics committee approval (E.C. 444/2021).

2.1 | D-OCT descriptors

For the evaluation of D-OCT images, qualitative and quantitative measurements were obtained. Two expert readers jointly retrospectively evaluated D-OCT parameters, as follows: infundibular hyperkeratinization, blurred dermal-epidermal junction (DEJ), granular epidermis, amorphous material inside follicles, organized inflammatory infiltrate, threshold at 300 μm, threshold at 500 μm (Table 1).

2.2 | Statistical analysis

Absolute and relative frequencies, mean and standard deviation (SD) for continuous measurements were calculated for each parameter. Frequencies and measurements of the D-OCT patterns were determined and the following comparisons were performed: (1) HS

TABLE 1 Definition of morphologic and vascular D-OCT features of HS nodules

D-OCT features	Definition
Infundibular hyper-keratinization	Thick linear hyper-echogenic signal that persists among the corneum and increases at the infundibulum
Blurred DEJ	Ill-defined dermal–epidermal junction (without defined boundaries)
Granular epidermis	Sand-like hypo-echogenic epidermis
Clots of amorphous material inside follicles	Hyper-echogenic plug inside the follicle
Organized inflammatory infiltrate	Collection of organized hyper-echogenic inflammatory material in the epidermis and the dermis
Threshold at 300 μm	The evaluation of the amount of red pixel at 300 μm from the stratum corneum corresponding to vessel density.
Threshold at 500 μm	The evaluation of the amount of red pixel at 500 μm from the stratum corneum corresponding to vessel density.

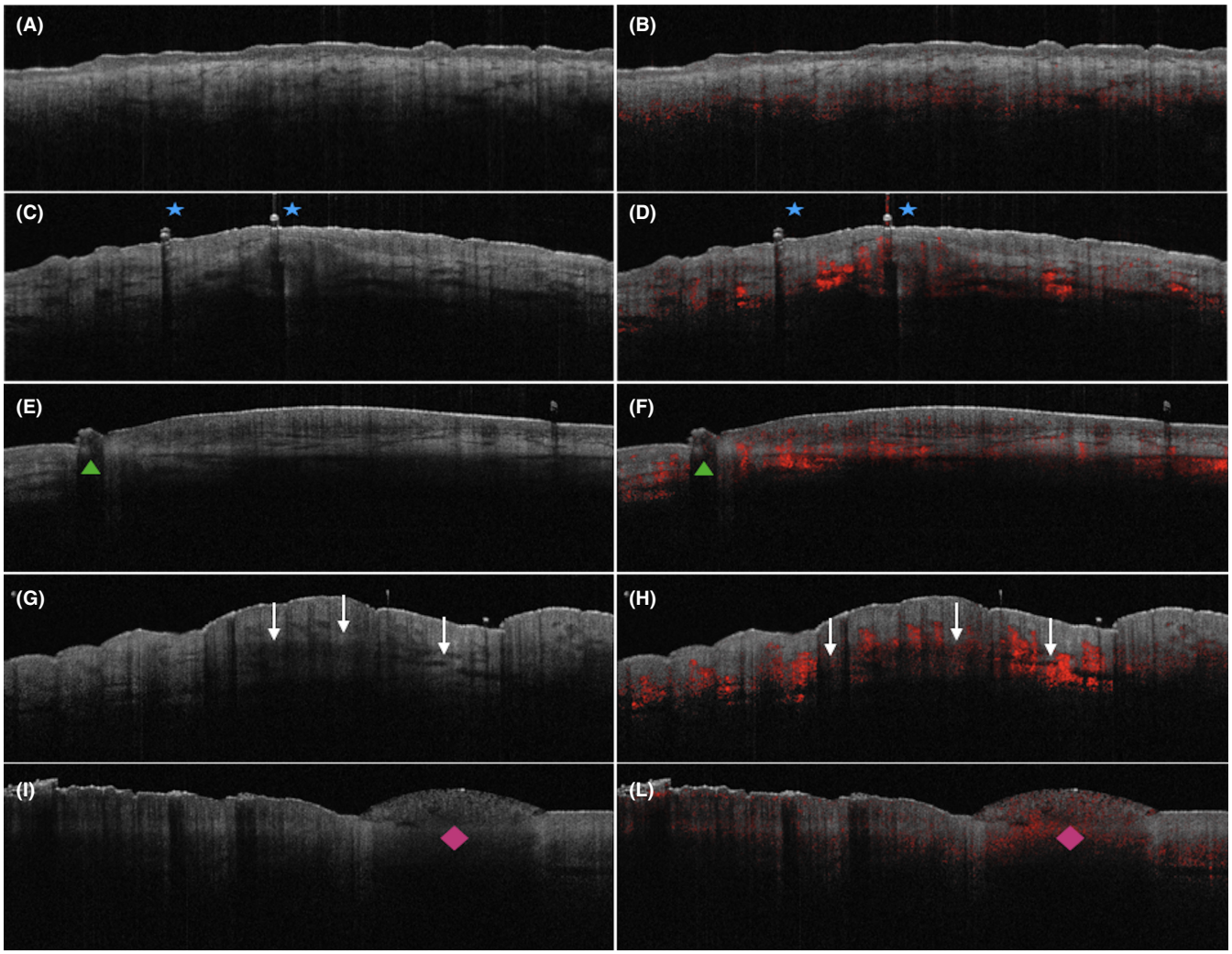

FIGURE 1 Cross-sectional OCT image of healthy axillary skin showing a normal epidermal thickness and a well-defined DEJ (A). Vascular D-OCT image of healthy control (B) with normal vascularization; Cross-sectional OCT image of HS nodule characterized by hyper-keratinization at the level of the infundibulum (blue stars) (C) and corresponding vascular D- OCT image showing increased vascular signal (D); Cross-sectional OCT image of HS nodule showing clots, characterized by amorphous keratinized material inside follicles (green arrowheads) (E) and corresponding vascular D-OCT image (F); Cross-sectional OCT image of HS nodule showing increased epidermal thickness, with papillomatosis (white arrows) and blurred DEJ (G). Vascular D-OCT image of increased epidermal thickness, with enlarged dermal papillae that project into the epidermis (H). Cross-sectional OCT image of HS nodule characterized by the presence of an organized inflammatory infiltrate, corresponding to a collection of organized hyper-echogenic inflammatory material in the epidermis and the dermis (pink rhombus) (I) and corresponding D-OCT image with increased vascular signal (L)

nodules vs control group healthy skin; (2) direct comparison between phenotypes (FP vs IP vs MP). Student T-test and Fisher exact test were calculated to compare continuous and nominal variables, respectively (SPSS v. 17 Inc., Chicago, IL, USA). Bonferroni adjustment was used (critical $\alpha = 0.05$) in order to control for Type I error for multiple comparisons. A p-value less than 0.00625 was considered significant.

3 | RESULTS

A total of 57 HS nodules was analysed with D-OCT from 40 mild-moderate HS patients of whom 40% were male. Patient's mean age was 33 years (range 11–73) and the mean BMI was 28.3 (range 17–38.1). Time from disease onset varied from 1 to 30 years (average: 8) before enrolment with paediatric onset was reported in 12 patients (30%). Most HS patients were active smokers (58%) and all patients had a history of multiple HS medical or surgical treatments, with subsequent recurrence. Disease severity, according to International Hidradenitis suppurativa Severity Score System (IHS4),[13] ranged from 2 to 20 (mean 9.6) with phlogistic lesions in two body sites for most of the patients (range 1–5). Disease flares were reported with an average of 2.4 episodes every 2 months (range 1–8 episodes). We observed an average value of the visual analogue scale (VAS) for pain of 7.2 (range 4.3–10.0). Data reported are summarized in Table S1.

Dynamic optical coherence tomography images showed that HS nodules compared to healthy skin were typically characterized by one or more hyper-keratinized infundibula at the top ($p < 0.005$) and a hypo-echogenic area in the dermis (Figure 1). The presence of amorphous material inside the infundibula and of an organized inflammatory infiltrate were often observed ($p < 0.005$). The contour of the dermal–epidermal junction was frequently ill-defined, probably due to inflammatory phenomena ($p < 0.005$). Average epidermal thickness was significantly higher in the border of HS nodules (203 μm, SD: 54 μm) compared with healthy skin (128 μm, SD: 19 μm). In D-OCT en-face images, the vascular signal of HS nodules was significantly increased with respect to the control group, both at 300 and 500 μm depths (Table 2, Figure 2).

Among the selected population of mild-moderate HS, 11 patients presented a mainly follicular phenotype (FP) with a longer disease duration (average 13 years) and the presence of inflammatory nodules without the tendency to coalesce, surrounded by open comedones. These patients reported a disease course characterized by a more indolent progression. Ten patients presented a mainly inflammatory phenotype (IP), characterized by a shorter disease duration (average 4 years), the absence of folliculitis/comedones in the affected areas, and the presence of tunnels and coalescing deep-seated nodules with scarring. Fifteen patients presented a mixed phenotype (MP), presenting both features of the previously described entities. The comparison of D-OCT images of nodules of FP and IP patients demonstrated a significant difference regarding the vascular threshold of the lesions at 500 μm depth, showing a higher blood flow and microcirculation in the nodules of IP patients with respect to FP patients (Figure 2).

TABLE 2 D-OCT features of HS nodules in comparison with healthy control skin from the same body regions

	Healthy control skin, $n = 20$				HS nodules, $n = 57$				
D-OCT features	**Average**	**SD**	**Count**	**%**	**Average**	**SD**	**Count**	**%**	***p*-value***
Vascular threshold at 300 μm	1755	1428			13068	14943			<0.001
Vascular threshold at 500 μm	13665	8198			47523	48191			<0.001
Epidermal thickness, mm	0.1284	0.0195			0.2033	0.0547			<0.001
Infundibular hyper-keratinization									
No			14	70%			7	12.3%	<0.001
Yes			6	30%			50	87.7%	
Blurred DEJ									
No			14	70%			16	28.0%	<0.001
Yes			6	30%			41	71.9%	
Granular epidermis									
No			19	95%			9	15.7%	<0.001
Yes			1	5%			48	84.2%	
Clots of amorphous material inside follicles									
No			18	90%			15	26.3%	<0.001
Yes			2	10%			42	73.7%	
Organized inflammatory infiltrate									
No			20	100%			14	24.6%	<0.001
Yes			0	0%			43	75.4%	

*A p-value less than 0.006 was considered significant due to Bonferroni adjustment.

4 | DISCUSSION

The characterization of morphological and functional features of HS nodules with OCT may be advantageous for the identification of anatomical and functional modifications to better understand disease pathogenesis and progression and to monitor the efficacy of HS therapy. The clinical appearance of a small, subcutaneous, painful, phlogistic nodules, located in typical or atypical body-sites, is the initial most common manifestation of HS, especially during the early stages of the disease (Hurley I and II).[10]

Dynamic optical coherence tomography images showed that HS nodules are morphologically and functionally significantly different from healthy skin: they present a dome shaped morphology with one or more enlarged infundibula at the top, with amorphous keratin material inside. The epidermis surrounding the nodule is generally thicker with respect to control healthy skin of the same body-sites and with a granular aspect, plausibly reflecting the presence of psoriasiform acanthosis.[7] Moreover, the contour of the dermal–epidermal junction is less defined, probably due to inflammatory phenomena.[28] In the dermis an anechogenic area is usually seen and, when the nodule is suppurating, the presence of hyperechogenic inflammatory amorphous material, inside the epidermis or in the superficial dermis, could be observed. HS nodules have increased vascular signal as demonstrated by the significant difference of the vascular threshold compared with the control healthy skin, both at 300 and 500 μm depths. This observation, which is explained by the induction of increased dermal blood flow and skin micro-vascularization caused by the phlogistic processes of HS, gives important information regarding the actual inflammatory status of the disease (Figure 1).

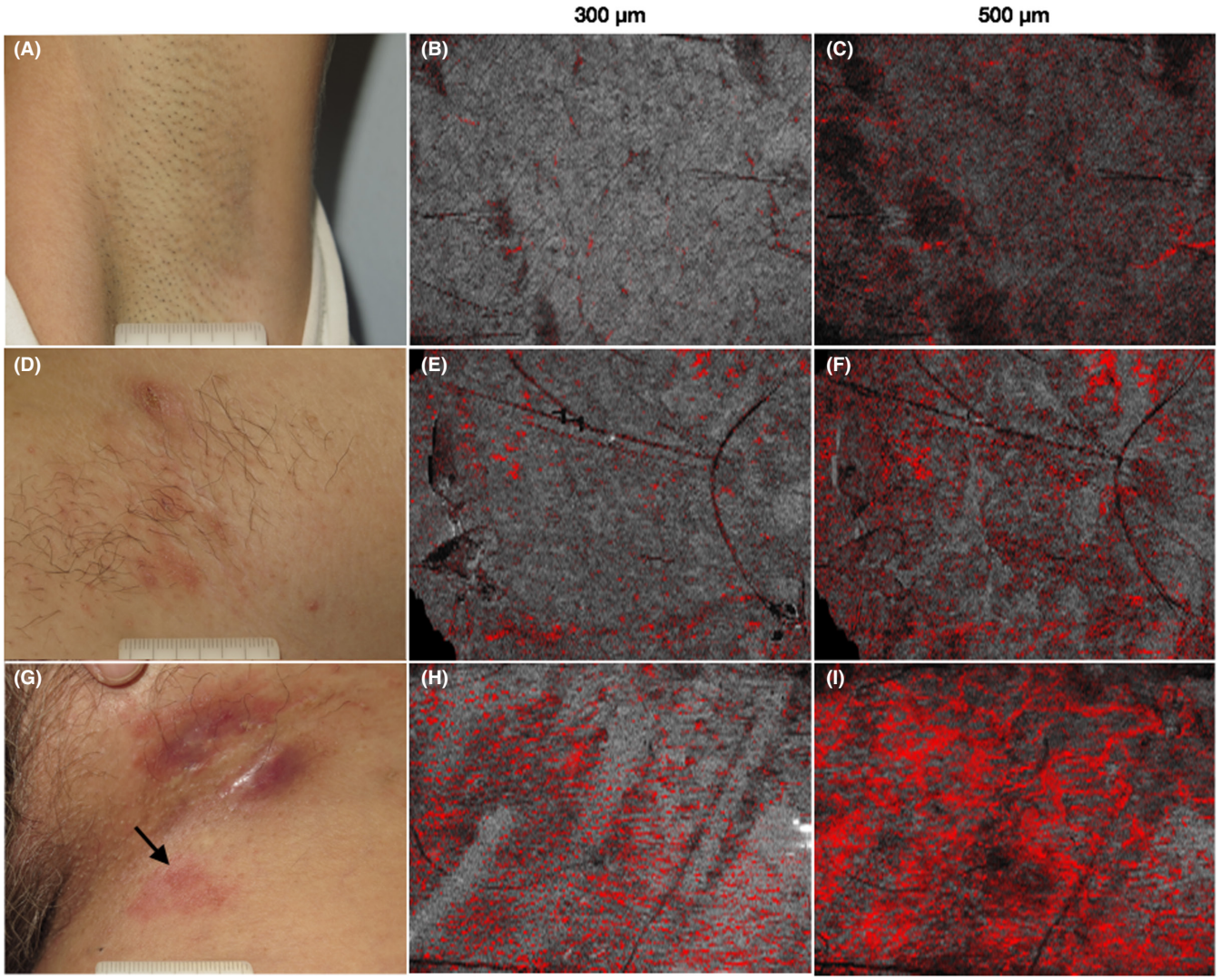

FIGURE 2 Clinical image of healthy control showing the absence of inflammation (A) and *en-face* D-OCT image showing a low vessel density, corresponding to low-threshold, at both 300 and 500 μm (B,C); Clinical image of an HS nodule from FP group of patients (D) and *en-face* D-OCT image showing higher vessel density compared to healthy control at both 300 and 500 μm (E,F). Clinical image of an HS nodule in the bottom part of the image (black arrow) obtained from a patient in the IP group (G) and *en face* D-OCT image at 300 and 500 μm showing significantly increased vessel density at 500 μm compared to follicular HS (H,I)

This data is in accordance with previous studies which demonstrated that HS lesions are characterized by widening of pilosebaceous units, the presence of a dermal fluid collection and the observation of a high power-Doppler ultrasound signal in the proximity of the lesions, which decrease after specific therapy, consistently with the resolution of the inflammatory processes.[29–33] In addition, the presence of widened and hyper-keratinized pilosebaceous units may reflect one of the leading events implicated in HS pathogenesis, which starts with an abnormal infundibular keratinization that causes occlusion and rupture of the follicular ostia.[30,34,35] Afterwards, HS inflammatory process is known to affect the microcirculation network initiating a remodelling process that ends in a vicious cycle of enhanced inflammation and scarring.[10,36]

In order to further characterize HS features, we compared nodules from FP and IP patients. This analysis showed a significant difference regarding the vascular threshold at 500 μm depth, implicating that IP nodules present a higher blood flow in the deep dermis with respect to FP nodules. This phenomenon could possibly represent a sign of enhanced inflammatory-shift of IP disease, with respect to FP, leading to the rapid development of more complex lesions. It is plausible to hypothesize that higher increase of blood flow values in IP nodules may be associated to a stronger local and systemic inflammation, inducing dermal tissue remodelling with subsequent generation of fibrotic processes, scarring, sinus tract formation and an augmented probability of other comorbidities as such as increased cardiovascular risk.[20]

Although further studies are required to correlate microscopic features with biologic data, D-OCT represents a useful tool for the in vivo skin investigation at nearly histologic resolution of HS lesions. In the near future, the morphologic and vascular alterations occurring during the initiation and maintenance of the disease will be monitored through non-invasive imaging procedures, for the better understanding and management of patients, allowing a precise quantification of therapeutic efficacy, as it has been shown in other inflammatory skin diseases.[22] To the best of our knowledge, Hurley's classification of HS is still the most applied in clinical practice, but it seems to be quite limiting in both diagnosis and follow-up of patients. Indeed, the identification of different HS phenotypes, through clinical examination and D-OCT imaging, could improve HS diagnosis and management, especially when atypical localizations or early disease presentation occur. A precocious and more aggressive treatment of HS patients with a rapidly evolving type of disease that corresponds to the IP phenotype is crucial to prevent the appearance of complex scarring with unfavourable disease course.

To conclude, the characterization of HS nodules through D-OCT image analysis allows to identify specific features associated with infundibular alterations, inflammation and tissue remodelling with neovascularization. The microscopic and functional analysis of early HS lesions with D-OCT may have important clinical consequences for patient assessment and management, and to non-invasively monitor treatment efficacy, in order to prevent scarring and disease progression.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Marco Manfredini, Giovanni Pellacani and Vincenzo Bettoli designed the study and wrote the paper. Camilla Chello and Silvana Ciardo collected D-OCT images and analysed data. Stefania Guida and Johanna Chester collected and elaborated data from literature. Marco Manfredini, Claudia Lasagni, Laura Bigi and Francesca Farnetani enrolled patients in the study and collected clinical data. All the authors have read and approved the final version of the manuscript. Authors declare that all procedures performed involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Tab S1. Epidemiological and clinical features of HS patients.

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