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Optical coherence tomography for patch test grading: A prospective study on its use for noninvasive diagnosis of allergic contact dermatitis

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Abstract

Background: The diagnosis of allergic contact dermatitis should be confirmed by skin patch tests. Distinguishing between irritant and allergic reactions is sometimes difficult.

Objectives: To analyse the in vivo morphological changes in patch test reactions compared to healthy skin, and to detect subclinical changes in doubtful reactions using optical coherence tomography (OCT). To develop an OCT-based algorithm to support patch-test grading.

Methods: One hundred twenty-nine skin patch-test areas were scanned with OCT to evaluate the following features: architectural and vascular morphology, epidermal thickness, optical attenuation coefficient (AC), and blood flow at 0.1, 0.2, and 0.35 mm depth.

Results: Most common OCT features of acute contact allergic reactions in patch tests were spongiosis with microvesicles (94.8%), macrovesicles (60.3%), and coalescing vesicles (46.6%), the latter useful in differentiating acute allergic from irritant dermatitis (P-value < .05). Objective quantitative parameters correlated well with the severity grade: epidermal thickness due to spongiosis, AC (P-value < .05) and blood flow at 0.2 and 0.35 mm (P-value < .01).

Conclusions: OCT as a noninvasive diagnostic tool, established for skin cancer diagnosis, is useful for evaluating contact allergic patch-test reactions. Not only morphological but also objective features such as blood flow and AC correlate with the reaction severity. Further studies are needed to explore the differences in irritant and allergic contact dermatitis.

KEYWORDS

contact allergy, dynamic OCT, noninvasive diagnostics, optical coherence tomography (OCT), patch-test grading

Eva Oppel and Elke Sattler (both senior authors) contributed equally.

1 | INTRODUCTION

Contact dermatitis to environmental allergens is a very common disease, with an estimated prevalence of 20% in the general population.[1] It describes a pattern of reaction of the skin to exogenous agents, caused either by a cell-mediated type IV immune response (allergic) or not (irritant or toxic). Histologically, a cutaneous inflammation occurs with spongiosis, vesicle-formation, and vasodilation in the acute phase, which can evolve to a chronic spongiotic dermatitis with hyperkeratosis, parakeratosis, irregular acanthosis, and elongation of the rete ridges. Even histology does not always allow a clear distinction between contact allergic and irritant or toxic dermatitis.[2]

The diagnosis is based on an accurate medical history and clinical examination followed by skin patch tests.[3] The latter represents the diagnostic gold standard and reproduces a contact allergy in an individual sensitized to a particular hapten. Standardized concentrations of allergens in an appropriate vehicle are applied in confined chambers to the skin of the back (rarely of the extremities) under occlusion. Reported specificity and sensitivity range between 70% and 80% depending on the tested substance.[4] According to the scoring system, developed by the International Contact Dermatitis Research Group (ICDRG), the reaction in patch testing is classified into six groups based on the specified morphological criteria, ranging from no reaction (0) to extreme positive bullous reaction (+++), with additionally doubtful (?+) and irritant reactions (IR).[5,6] A drawback of patch testing is that the interpretation of the results is usually influenced by the observer; hence it is not fully objective.[5,7,8] Another issue is the difficulty in distinguishing especially + allergic reactions from weak irritant contact dermatitis, since erythema and infiltration are present in both cases.

Various diagnostic modalities have been investigated in attempts to overcome the subjectivity of patch test grading, and among them are laser Doppler velocimetry, transepidermal water loss, colorimetry, infrared thermography, 20-MHz ultrasound A-Scans, high-definition optical coherence tomography, optoacoustic mesoscopy, dermoscopy, reflectance confocal microscopy (RCM) and conventional optical coherence tomography (OCT).[9-16] OCT is a noninvasive imaging technique that can differentiate skin structures, including the stratum corneum, the epidermis, the upper dermis, skin appendages, and blood vessels. It is particularly suitable for the diagnosis of epithelial skin tumors and monitoring of resolution/persistence/relapse/progression following nonsurgical therapies, but it is also used in inflammatory and infectious diseases.[17] In this prospective study, we examined the in vivo morphological changes of skin patch tests in a cohort of 129 skin areas using standard and dynamic OCT. The aim of this study was to analyze the morphological skin changes in vivo in acute allergic and irritant contact dermatitis compared to healthy skin, and eventually to detect subclinical changes in unclear reactions. Furthermore, we aimed at developing an OCT-based algorithm for additional objective parameters in patch-test grading to support clinical evaluation especially in doubtful reactions.

2 | MATERIALS AND METHODS

OCT images sized 6 mm × 6 mm down to a skin depth of about 1 to 1,5 mm were acquired using the commercially distributed Vivosight (Michelson Diagnostics, Maidstone, Kent, UK). This frequency domain OCT is based on Michelson interferometry, has a lateral optical resolution of 7.5 μm, and an axial resolution of 10 μm, combined with a penetration depth of up to 1 to 1.5 mm. Its laser source (HSL 2000; Santec Corporation, Komaki, Japan) has a wavelength of 1305 nm. The device has a handheld probe, which is provided with a series of plastic spacers to adjust the focus to different skin sites. The dynamic mode allows the visualization of blood flow and vessels simultaneously with morphologic features of the tissue. A more detailed description of the device is provided elsewhere.[18]

Patients with suspected allergic contact dermatitis undergoing patch testing in our allergy outpatient department were enrolled in the study. Patch testing was performed according to the international and German guidelines on the upper back and removed after 48 hours. Conclusive grading was performed following the German guidelines after 3 days, and also after 7 or 10 days for aminoglycosides, *p*-phenylenediamine, and metals.[6]

A total of 129 skin areas from 29 patients with positive patch-test reactions (10 male and 19 female, mean age 48.5, range 22 to 80 years) (Supplementary Table S1) in our allergy department were scanned in both en face and dynamic mode with OCT. Seventy-three positive (44 +, 27 ++, 2 +++), 16 unclear, 16 irritant reactions to sodium lauryl sulfate (SLS), and 23 healthy skin controls were acquired. Every area was evaluated in its center by three dermatologists blinded to the clinical diagnosis. Good interobserver agreement was found for all parameters (Cohen's kappa coefficient: 0.7); disagreements were solved by the involvement of a fourth senior dermatologist. The following morphologic OCT features were analyzed: OCT spongiosis was characterized by enlarged interkeratinocyte spaces, blurred dermo-epidermal junction (DEJ), pustules, erosions, bright spots, and epidermal vesicles (subcorneal or deep intraepidermal). Vesicles were subdivided arbitrarily into microvesicles (smaller than 0.1 mm), not always clearly distinguishable from enlarged interkeratinocyte spaces in a spongiotic epidermis due to OCT spatial resolution, and macrovesicles (larger than 0.1 mm). Further analyzed features included superficial and deep vasodilation and vascular morphology in en face and dynamic. Epidermal thickness was computed based on an average of 10 repeated measurements, and the OCT software calculated this average.

The optical attenuation coefficient (AC) and blood flow analysis were calculated using the software tool "OCT Analyse-OCT research tool" provided by Michelson Diagnostics. Optical AC corresponds to the average OCT signal related to depth across the whole scan and can be interpreted as a marker for signal disruption. Capillary blood flow is quantified by calculating the signal intensity of speckle variance produced by local movement (=dynamic) at different depths. Objective measurements of blood flow from 0.1 to 0.35 mm from the skin surface in 0.5 mm intervals were obtained.

For statistical analysis, continuous variables were described by mean, standard deviation, and 95% confidence interval by total sample and by reaction grades. Blood flow at 0.1 mm, 0.20 mm, and 0.35 mm; ACs, and epidermal thickness were compared across the different reaction grades and the healthy skin using one-way analyses of variance (ANOVAs). To compare the categorical variables, we used the chi-square test of independence. Statistical significance was determined at the level of *P*-value < .05. All statistical analyses were completed using IBM SPSS Statistics.

The study was conducted according to the principles of the Declaration of Helsinki and international guidelines concerning human studies. It was approved by the local ethics committee (Nr.17-699), and written informed consent was obtained from each subject.

3 | RESULTS

The following OCT patterns were evaluated: macro- and micromorphologic features, grading, vascular pattern, blood flow measurements, and AC (Table 1).

3.1 | Morphologic patterns

A blurred (interrupted) DEJ was visible in 33.3% of +, 83.3% of ++, 100% of +++ positive patch-test reactions and in 42.9% of irritant reactions in comparison to healthy skin (4.3%), thus positively correlating to the clinical grade (*P* < .01).

Microvesicles were present in 87.9% of positive patch-test reactions (84.4% of 1+, 91.7% of 2+, 100% of 3+), 80.0% of IR, and 13.0% of healthy skin. OCT spongiosis was found in 91.4% of positive patch test reactions (87.5% of 1+, 95.8% of 2+, 100.0% of 3+), 93.3% of IR, and 17.4% healthy skin. Clustered together, they were present in 94.8% of positive patch-test reactions (93.8% of 1+, 95.8% of 2+, 100.0% of 3+), 93.3% of IR, and 26.1% of healthy skin. There was a statistically significant difference compared to healthy skin (*P* < .01) but not between contact allergic patch-test reactions (reproducing allergic contact dermatitis [acute allergic contact dermatitis (ACD)]) and IR (*P* < .082).

Macrovesicles (60.3% of positive reactions vs 26.7% of IR) and deep vesiculation at the level of lower stratum granulosum and stratum spinosum (46.6% of positive reactions vs 13.3% of IR) were statistically significantly more frequently detected in positive patch test reactions compared to irritant contact dermatitis induced by SLS (*P* < .05) (Figures 5 and 6). Deep blistering (near the DEJ) was present in 46.6% of positive patch-test reactions compared to 13.3% of IR and 0.0% of healthy skin, significantly differing in all groups (*P* < .01).

Erosions were found in 19.0% of positive patch-test reactions (15.6% of +, 25.0% of ++, 0.0% of +++), 26.7% of IR, and 0.0% of healthy skin. Pustules appeared in 53.4% of positive patch-test reactions (40.6% of +, 70.8% of ++, 50.0% of +++), 26.7% of IR, and 4.3% of healthy skin. Bright spots were found in 86.2% of positive patch-test reactions (81.3% of +, 91.7% of ++, 100.0% of +++), 93.3% of IR, and 8.7% of healthy skin. The above-mentioned parameters did not differ significantly between contact allergic positive patch-test reactions and IR (Figure 1).

3.2 | Vascular pattern

The following vascular patterns were analyzed: arborizing vessels, serpiginous vessels, linear vessels, dotted vessels, superficial vasodilation, and deep vasodilation. Large serpiginous vessels (64.3% of positive patch tests vs 15.8% of healthy skin), as well as superficial (89.7% of positive patch tests vs 34.8% of healthy skin) and deep vasodilation (47.4% of positive patch tests vs 8.7% of healthy skin), were significantly more represented in positive patch test reactions compared to healthy skin (*P* < .01). Of interest, large serpiginous vessels were significantly more frequent in irritant reactions compared to healthy skin (50.0% vs 15.8% respectively, *P* < .035).

3.3 | Epidermal thickness

Mean epidermal thickness was 0.152 mm (± 0.053), (0.173 mm ± 0.057 in positive patch tests vs 0.144 mm ± 0.025 IR vs 0.108 mm ± 0.017 in healthy skin) (Figure 2A). Significantly higher epidermal thickness, increasing with the clinical grade (Figure 2B), was

TABLE 1 Mean epidermal thickness (EC) in mm, cutaneous blood flow rate in mm/s, and attenuation coefficient in examined positive patch-test reactions (ACD), also subdivided by clinical grading (+, ++, +++), irritant reactions (IR), and healthy skin controls

			Mean cutaneous blood flow rate (mm/s)			
Site reaction		Mean epidermal thickness (mm)	At 0.1 mm depth	At 0.2 mm depth	At 0.35 mm depth	Attenuation coefficient
ACD	Global	0.1733 ± 0.0575	0.0230 ± 0.0430	0.0587 ± 0.0494	0.1628 ± 0.0686	1.7200 ± 0.3299
ACD	+	0.1521 ± 0.0512	0.0133 ± 0.0132	0.0403 ± 0.3355	0.1456 ± 0.0764	1.7737 ± 0.2548
ACD	++	0.1967 ± 0.0515	0.0341 ± 0.0626	0.0807 ± 0.0583	0.1802 ± 0.0566	1.6539 ± 0.4017
ACD	+++	0.2350 ± 0.0919	0.0325 ± 0.0348	0.0590 ± 0.0514	0.1798 ± 0.0280	1.45
IR		0.1440 ± 0.0256	0.0081 ± 0.0039	0.0265 ± 0.0155	0.1082 ± 0.0415	1.7177 ± 0.2053
Unclear		0.1420 ± 0.0443	0.0125 ± 0.0106	0.0409 ± 0.0304	0.1346 ± 0.0544	1.8775 ± 0.2121
Healthy skin		0.1516 ± 0.0526	0.0084 ± 0.0114	0.0195 ± 0.0121	0.0998 ± 0.0338	1.9086 ± 0.2248

Abbreviation: ACD, acute allergic contact dermatitis.

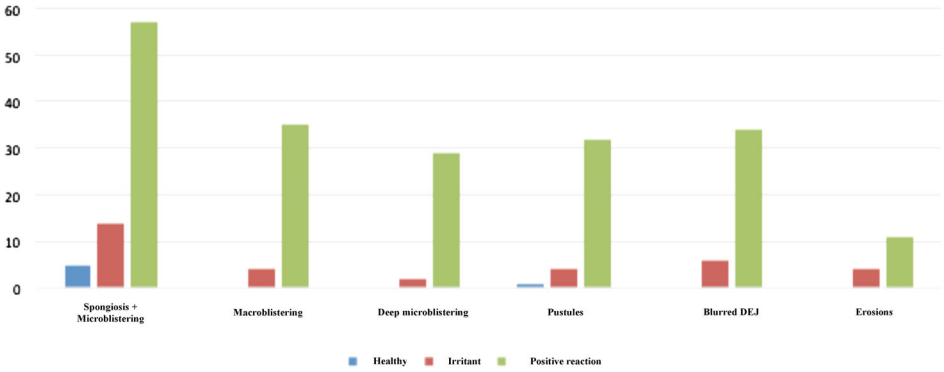

FIGURE 1 Frequency of morphological optical coherence tomography features of examined positive patch-test reactions, irritant reactions, and healthy skin controls

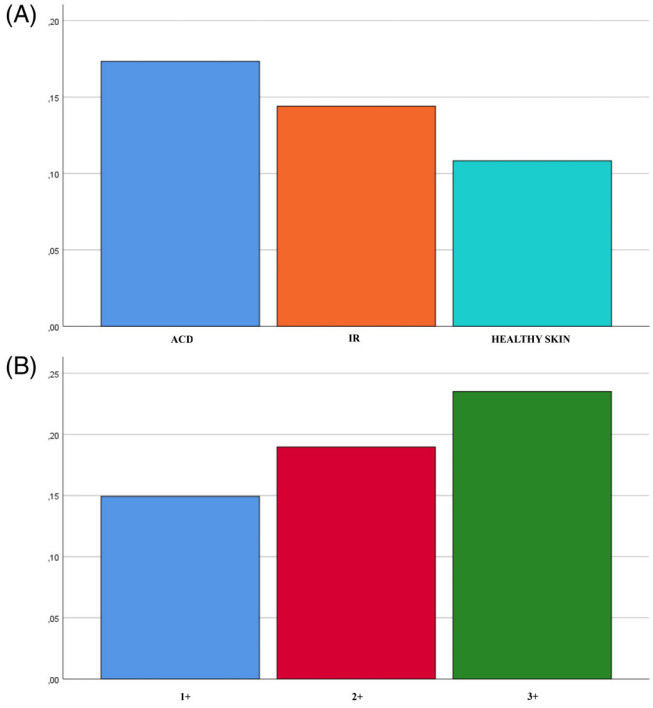

FIGURE 2 Mean epidermal thickness in mm measured by optical coherence tomography in (**A**) examined positive patch-test reactions (ACD), irritant reactions (IRs), and healthy skin controls. (**B**) Examined positive patch-test reactions subdivided by clinical grading (+, ++, +++)

observed in positive patch-test reactions (0.152 mm ± 0.052 in 1+, 0.197 mm ± 0.051 in 2+, 0.235 mm ± 0.092 in 3+) ($P < .01$). The difference was statistically significant, also compared to healthy skin ($P < .05$).

3.4 | Cutaneous blood flow rate at a depth of 0.1 mm

Mean cutaneous blood flow rate at a depth of 0.1 mm was 0.0167 ± 0.0329 mm/s (0.0230 ± 0.0430 in contact allergic patch test reactions and 0.0081 ± 0.0037 in IR and 0.0084 ± 0.0114 in healthy skin) (Figure 3A) There was no significant difference across the different clinical groups ($P = .083$) (Figure 3B).

3.5 | Cutaneous blood flow rate at a depth of 0.2 mm

Mean cutaneous blood flow rate at a depth of 0.2 mm was 0.0441 ± 0.0419 mm/s (0.0587 ± 0.0430 in contact allergic patch test reactions, 0.0265 ± 0.0155 in IR and 0.0195 ± 0.0121 in healthy skin) (Figure 3A). A statistically significant difference between all clinical grades ($P < .01$) and compared to healthy skin was recorded (Figure 3B).

3.6 | Cutaneous blood flow rate at a depth of 0.35 mm

Mean cutaneous blood flow rate at 0.35 mm was 0.1388 ± 0.0638 mm/s (0.1628 ± 0.0686 in contact allergic patch test reactions, 0.1059 ± 0.0406 in IR and 0.0998 ± 0.0338 in healthy skin) (Figure 3A) It significantly increased proportional to the clinical grade from 1+ to 2+ ($P < .01$) (Figure 3B).

3.7 | Attenuation coefficient

Mean AC was 1.781 ± 0.292. There was a statistically significant difference in AC among all groups ($P < .05$), with a mean value of 1.73 in positive patch tests, 1.72 in IR reactions, and 1.91 in healthy skin (Figure 4A). AC was statistically significantly lower ($P < .01$) in positive patch-test reactions compared to healthy skin, and was inversely related to the grading (1.77 in + reactions, 1.66 in ++ reactions, 1.45 in +++ reactions) ($P < .05$) (Figure 4B).

3.8 | OCT grading

An OCT grading of patch-test reactions was performed, based on the criteria for clinical evaluation of patch testing. OCT spongiosis and microvesicles were graded with +, macrovesicles with ++, and coalescent vesicles with +++ (Figure 5). The re-evaluation resulted in a higher grading in 54.6% of + cases and 66.7% of ++ cases. Lower grading occurred in 6.1% of +, in 8.4% of ++, and 50% of +++ positive

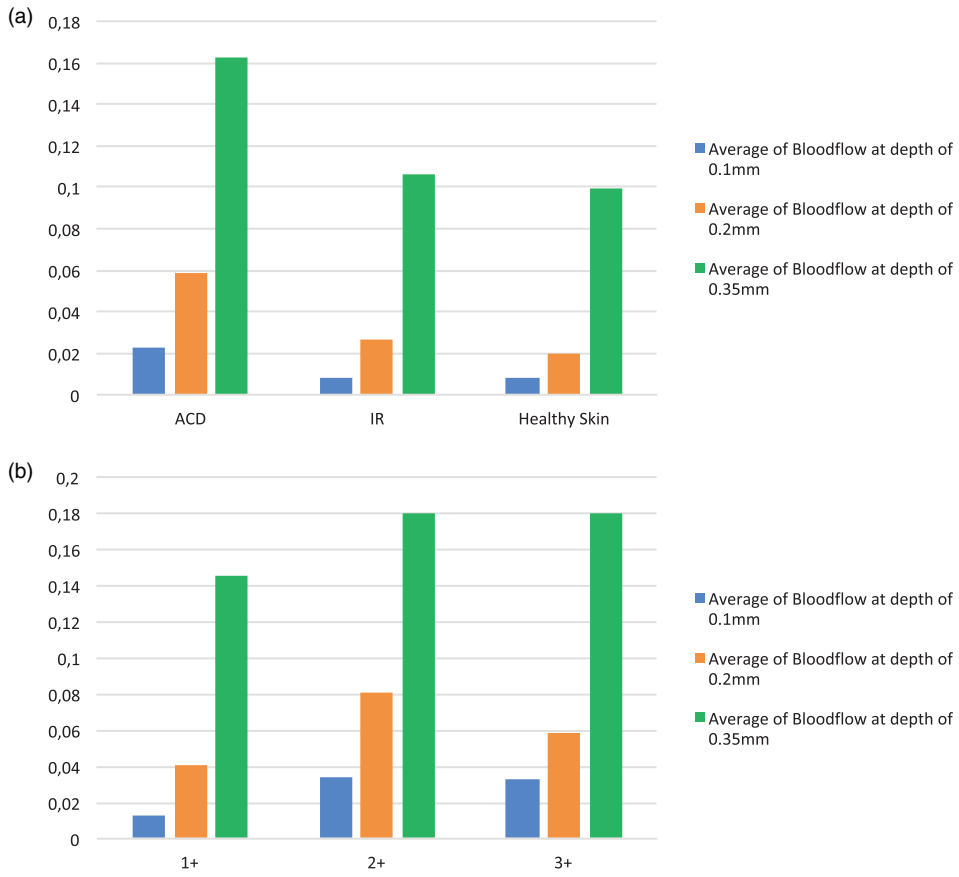

FIGURE 3 Mean cutaneous blood flow rate at different depths (0.1, 0.2, 0.35 mm) measured by dynamic optical coherence tomography in (**A**) examined positive patch test reactions (ACD), irritant reactions (IRs), and healthy skin controls. (**B**) Examined positive patch-test reactions subdivided by clinical grading (+, ++, +++)

patch tests. All clinically unclear lesions could be OCT graded, with no reaction (grade 0) in 13.3%, + in 20%, ++ in 20%, and +++ in 46.7%.

4 | DISCUSSION

Patch-test reactions are assessed by visual inspection, supported by palpation, and based on morphological clinical criteria (erythema, infiltration, papules, vesicles, confluent vesicles).[5,6,19] However, even reactions classified as positive could turn out to be irritant, so that a clinical follow-up after 1 or 2 days may be required. To detect an increased skin irritability at the time of testing, the German standard patch-test series includes sodium lauryl sulfate 0.25% aq. as an irritant control to use as a comparison for unclear reactions.[6] Thus it can be difficult to properly grade patch-test reactions, especially in doubtful cases, and interobserver variability even among expert readers is unavoidable.

Since surgical biopsies are painful, expensive and time-consuming, and histopathology does not always allow a precise distinction between contact allergic and irritant patch test reactions, various noninvasive diagnostic techniques were used to further investigate patch test reactions experimentally.[15,16,20-23] Dermoscopy is cheap and available worldwide; pilot studies correlated erythema, vesicles, orange-yellowish patchy areas, and vessels with allergic reactions compared to irritant reactions; nonetheless, additional studies on doubtful reactions are needed.[15,16] Among further noninvasive diagnostic tools, RCM, OCT, and optoacoustic mesoscopy showed the most promising results.[9-14,24] However, RCM is more time consuming than OCT and does not provide an immediate, intuitive comparison with histology in nonexpert physicians. Optoacoustic mesoscopy was able to associate a higher fragmentation of skin vasculature and a lower ratio of low-to-high frequency acoustic signals to allergic reactions compared to irritant reactions in a pilot study[24]; however, use of the device is still limited to clinical research. The few studies with OCT reported to date were based on a small number of samples and did not systematically include irritant controls and unclear reactions. Gamblicher et al analyzed 20 positive patch-test reactions with the high-definition OCT by AGFA (not commercially available anymore), observing pronounced skin folds, thickened and/or disrupted entrance signals, increase in epidermal thickness, and clearly demarcated signal-free cavities within the epidermis with considerable reduction of dermal reflectivity.[10] Our group observed OCT morphological correlations to patch-test grading in five nickel-positive patients, detecting increased entrance signal and epidermal thickness compared to healthy areas, acute OCT spongiosis and vesiculation, vasodilation, and an edema in the papillary dermis visible as lower dermal reflectivity.[13] The University of Miami studied seven patients and identified a significant increase of the AC and of cutaneous blood flow at a 0.35-mm depth from 0 to ++.[12]

In the current study, we examined +, ++, and +++ patch-test reactions, together with IR and unclear reactions, and compared them to healthy skin. Allergic and irritant contact dermatitis share common

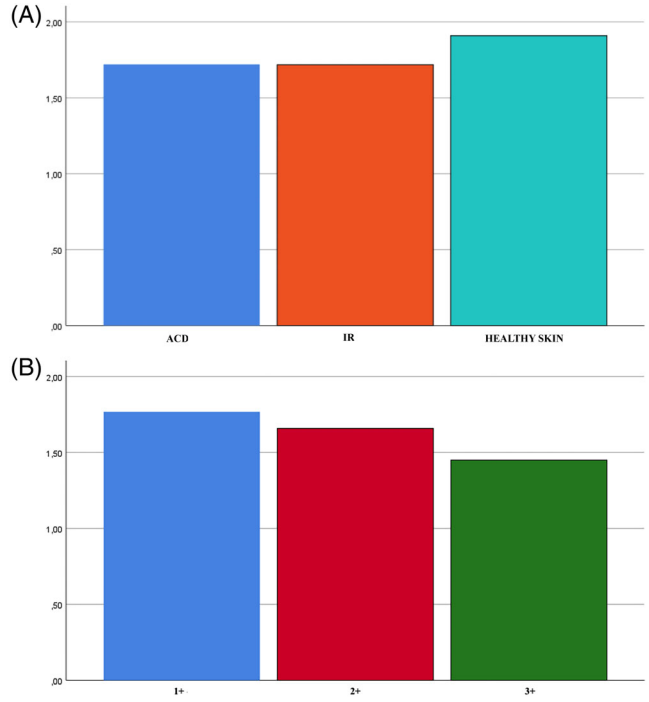

FIGURE 4 Mean attenuation coefficient (AC) measured by optical coherence tomography in (**A**) examined positive patch-test reactions (ACD), irritant reactions (IRs), and healthy skin controls. (**B**) Examined positive patch-test reactions subdivided by clinical grading (+, ++, +++)

histopathological features, such as epidermal spongiosis and intraepidermal vesicle formation as well as inflammatory cell infiltration in dermis and epidermis. However, spongiosis, exocytosis, and vesicles or bullae formation due to confluence of vesicles are more common and evident in allergic contact dermatitis. Focal epidermal infiltration and mononuclear perivascular infiltration in the dermis are common findings in allergic and irritant contact dermatitis. Such infiltrates may sometimes be associated with dilation of lymphatic or blood vessels. In irritant dermatitis, necrosis and pustules are more frequently observed and the perivascular infiltrate can vary from mononucleated to multinucleated. Edema and spongiosis are less common in irritant than in allergic dermatitis.[25]

Intuitively, an increase in epidermal thickness (ET) due to spongiosis and vesicle formation in acute allergic contact dermatitis is expected. We registered a statistically significant difference in ET measured by OCT, also in line with previous observations.[10] Average ET was significantly lower ($P < .01$) in healthy skin compared to positive patch-test reactions and positively correlated to patch-test grading. Surprisingly, ET in IR significantly diverged from both healthy skin and positive patch test reactions ($P < .05$), the average ET being halfway between positive reactions and IR.

Concerning macroscopic OCT patterns, we found spongiosis, blistering, pustules, bright spots, erosions, and poorly defined DEJ to be statistically significantly prevalent in acute contact dermatitis and IR compared to healthy skin ($P < .01$). Acute spongiosis (intercellular edema, due to abnormal accumulation of fluid) is visible as increased ET, brighter keratinocytic contours, darker enlarged intercellular spaces, and microvesicles. These were not always clearly distinguishable from enlarged interkeratinocyte spaces, due to OCT spatial resolution. Vesicles appeared in general as roundish low-signal cavities in the epidermis, variable in size, and sometimes containing bright material (corresponding to acantholytic cells and inflammatory infiltrate). They could coalesce in ++ and +++ patch-test reactions and tended to be also localized in the deeper epidermis in ++ and +++ patch-test reactions. Pustules were clearly localized as subcorneal or epidermal cavities filled with bright material, sometimes totally filled. Erosions were rarely visible. In our analysis, the presence of macrovesicles and deep vesiculation in the lower stratum granulosum and stratum spinosum was statistically significantly higher in positive patch-test reactions compared to irritant contact dermatitis induced by SLS ($P < .05$) (Figures 5 and 6).

Because OCT does not provide a cellular resolution, it is not possible to identify single inflammatory cells. However, it is hypothesized that conglomerates of them are visible as bright spots in the epidermis; this remains uncertain as also sweat ducts and parakeratotic nucleated cells have been described as bright spots previously.[26]

Probably due to the spongiosis and the resulting altered signal transmission to the dermis, both deep vasodilation and the DEJ were difficult to visualize in positive patch tests and in irritant reactions compared to healthy skin. A blurred DEJ positively correlated with the clinical grade; as a matter of fact it was barely visible not only in presence of macrovesicles but also in lower grade reactions with spongiosis and microvesicles.

A morphological analysis of blood vessels found that dotted vessels were present in all types of lesions. Linear and large serpiginous vessels en face were significantly more frequently represented in positive reactions compared to healthy skin ($P < .05$). In vertical mode, we observed a significant prevalence of superficial vasodilation in positive reactions compared to healthy skin ($P < .05$). We reported a prevalence of small and large serpiginous vessels in IR, although not significantly differing from positive reactions; large serpiginous vessels were significantly more frequent in IR compared to healthy skin ($P < .05$).

Every operator dependent technique, also OCT a (especially concerning the evaluation of morphological features) is subject to interobserver variability; hence, some objective parameters can complement the investigation. For example, speckle variance analysis is of outmost importance for a correct interpretation of blood flow, since massive interpersonal variability associated with disturbing factors (such as the immediate effect of pressure through the OCT probe, the occlusive effect of patch tests, sweating, palpation) negatively influences the visual assessment.

In the speckle variance analysis, OCT blood flow at 0.2 mm and at 0.35 mm depth (upper dermis) was significantly higher in ECT positive patch tests compared to IR reactions ($P < .01$) and healthy skin ($P < .01$). However, IR reactions could not be further distinguished from healthy skin or unclear reactions. We did not find any statistically significant differences in the blood flow analysis at a depth of 0.1 mm, probably due to the influence of the above-discussed external factors such as the pressure of the OCT detector during the examination.

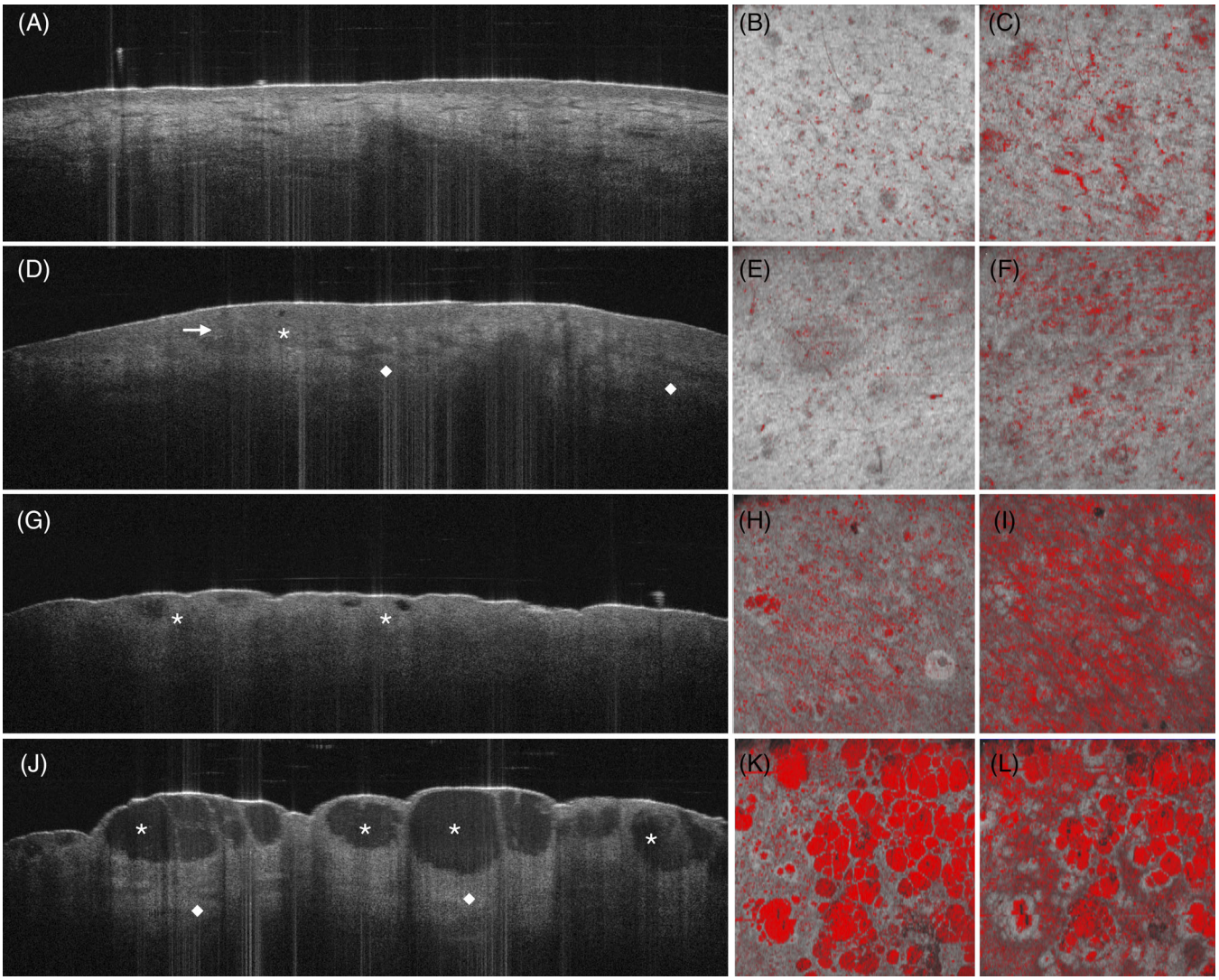

FIGURE 5 Optical coherence tomography (OCT) images in en face (left) and in en coupe dynamic modus at 0.2 mm (middle) and at 0.35 mm (right) depth of: one healthy control site (**A**-**C**) and three patients with allergic contact dermatitis with a positive patch-test grade + (**D**-**F**), ++ (**G**-**I**), and +++ (**J**-**L**). Note the difference between the healthy skin layers of the first patient (**A**) with regular epidermis and normal vascularisation pattern (**B**,**C**), and the mild positive reaction where acute spongiosis (arrow), vesicle formation (star), and vasodilation (diamond) can be identified in OCT (**D**-**F**). Those features, discrete as microvesicles and spongiosis in grade + patch-test reactions (**D**), are more evident in strongly positive clinical reactions (**G**,**I**) and clearly visible as coalescent vesicles (**J**) and pronounced vasodilation (**K**,**L**) in the last patient

Optical AC is also emerging as an important tissue parameter for measuring how quickly incident light is attenuated when passing through a medium, and this is a function of the underlying medium properties. Loss of light in tissue can be caused by absorption, scattering, or a combination of both.[27] It was hypothesized that homogeneous and healthy tissue has a higher AC compared to pathologic tissue. In fact, AC was statistically significantly lower ($P < .01$) in positive patch-test reactions compared to healthy skin and also inversely correlated with the grading of patch-test reactions. It did not significantly differ between IR and contact allergic patch-test reactions.

Based on our morphological observation, we performed a retrospective OCT grading of patch-test reactions included in the study, following the known criteria for clinical evaluation (Figure 5). OCT helped us detect clear-cut features of allergic contact dermatitis, such as spongiosis and microvesicles, macrovesicles, and coalescent vesicles. This more objective re-evaluation resulted in a higher patch-test score in over 50% of + and ++ patch-test reactions and enabled us to assign a grade to all clinically unclear lesions.

Our study confirmed the hypothesis that OCT is not only useful in the diagnosis and management of skin cancer but also in a broader spectrum of skin diseases. The device is helpful in differentiating allergic contact dermatitis and contact allergic patch-test reactions from unaffected healthy skin, since main histomorphological correlates are visible. The most important features here are spongiosis with microvesicles, macrovesicles, and coalescing vesicles. In particular,

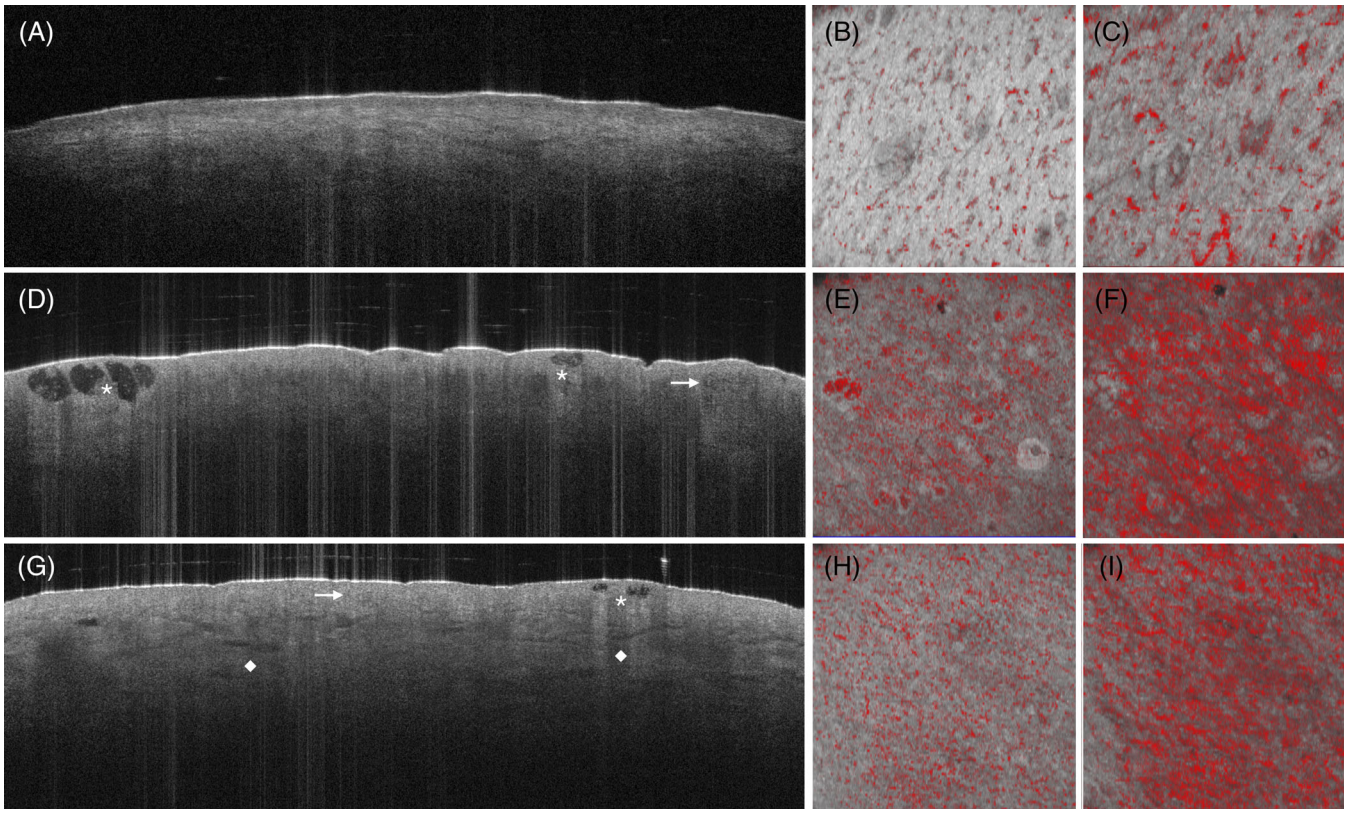

FIGURE 6 Optical coherence tomography (OCT) images in en face (left) and in en coupe dynamic modus at 0.2 mm (middle) and at 0.35 mm (right) depth of two patients with clinically unclear patch-test reactions (**A**-**F**) and one with irritative dermatitis due to sodium lauryl sulfate (**G**-**I**). **A**-**C** shows a reaction that was scored in OCT as negative, being comparable to healthy skin, whereas **D**-**F** shows a clearly positive reaction with OCT spongiosis (arrow), macrovesicle formation (star), and vasodilation (diamond). Irritative contact dermatitis typically shows microvesiculation, OCT spongiosis (**G**), and a dotted-serpiginous hypervascularization pattern

macrovesicles and deep blistering could help distinguish acute allergic from irritant dermatitis. OCT can also be used for more objective patch test grading, also thanks to additional operator-independent quantitative measurements, such as the analysis of blood flow at 0.2 and 0.35 mm and the AC. In addition, increased ET due to spongiosis is easy to measure and correlates well with the severity grade. Further studies are needed to explore the differences in irritant and allergic contact dermatitis and to further develop standardized diagnostic algorithms for OCT-aided patch test grading, especially in weak and doubtful positive reactions.

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AUTHOR CONTRIBUTIONS

Cristel Ruini: Idea, Patient recruitment, Conceptualization, formal analysis, supervision, validation, writing-review and editing.**Farnaz Rahimi:** Data curation; formal analysis; software. **Zeno Fiocco:** Data curation; visualization. **Lars French:** Project administration; validation; writing-review and editing. **Daniela Hartmann:** Formal analysis; writing-review and editing. **Eva Oppel:** Conceptualization; supervision; writing-review and editing. **Elke Sattler:** Conceptualization; formal analysis; supervision; validation; writing-review and editing.

CONFLICT OF INTEREST

All authors declare to have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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