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In Vivo Observation of Allergic Dermatitis of the Genuine Pig by Optical Coherence Tomography

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Abstract

In order to understand pathogenic mechanism of allergic dermatitis, it is important to find morphological changes of the internal structure of the skin by non-invasive imaging. Optical coherence tomography (OCT) is powerful tool for *in vivo* tomographic imaging of the internal microstructure in biological tissue. In this study, we prepared the animal model of genuine pig with allergic dermatitis developed by chemical administration to examining their skin inflammation by microscopic observations with OCT images captured continuously, aiming at tracking the morphological changes in the skin structure induced by the chronological inflammation. As a result, epidermis thickening became evident as the days passed since Day 7, and the capillary vessel expansion was confirmed since Day 14; the process of inflammation development was successfully observed.

Keywords

OCT, Allergic Dermatitis, *In Vivo* Observation, Thickening of Epidermis

1. Introduction

Various recent studies have suggested that every one out of three Japanese people has allergic conditions, and more than half of the adult population, especially younger adults, has developed an atopic constitution [1]. Patients with atopic dermatitis are estimated to consist approximately 10% of the population, yet direct causes of atopic and other allergic dermatitis have mostly remained elusive [2] [3] [4]. The situations in many western nations and other advanced nations are probably the same as seen in Japan, showing a trend in yearly patient number increase, onset age decrease, and an increase in the number of various allergy-causing substances [5] [6]. Therefore, non-invasive tracking of the morphological changes in the skin's internal structure should be essential for elucidating

the onset mechanism of allergic dermatitis.

The pathological tissue test is usually employed as the primary option in the morphological evaluation of the skin's internal structure, while other imaging apparatus, such as Optical Coherence Tomography (OCT) [7], confocal microscopy, and ultrasound imaging, are recently drawing attention. These imaging apparatus share advantages of being non-invasive and enabling follow-ups. Among these, OCT is capable of capturing tomographic images of skin subepidermal structure at a depth of 1 to 2 mm in a high resolution of approximately 10 μm; its first clinical application was implemented in the ophthalmic field, followed by various applications in the other medical practices, including dermatology [8], cardiology, digestive surgery, and dentistry. More recently, high-definition OCT has developed with cellular resolution filling the imaging gap between confocal microscopy and conventional OCT [9] [10].

Few studies have reported cases of non-invasive observation on the inflammatory process in allergic dermatitis. In this study, we prepared animal models with allergic dermatitis developed by chemical administration to examining their skin inflammation by microscopic observations with tomographic images captured continuously, aiming at tracking the morphological changes in the skin structure induced by the chronological inflammation. The results expected in this study would provide valuable information regarding structural/histological alteration in the skin during the development process of dermatitis. Here, OCT observation results on morphological changes in the skin during an allergic reaction and their daily variations since the onset date are discussed in this paper.

2. Experimental Method

2.1. Protocol of the Allergic Dermatitis-Inducing Model

Four guinea pigs at 4-weeks of age (male, weights of 250 to 300 g) were used as the animal model. They were put under constant temperature and humidity with free access to solid feed and water. **Figure 1** shows the procedure to prepare the allergic dermatitis-induced model animal [11]. First, 30 mg immunosuppressive agent was administered intraperitoneally, followed by the intraperitoneal administration of the egg allergy antigen, ovalbumin (OVA), mixed with an adjuvant. We set the date of the intraperitoneal administration as Day 0. Next, 20 mL of OVA was nasally administered to each model to sensitize or induce allergic reactions on the imaging day. The experiment was conducted on the guinea pigs, shaved and conditioned with depilatory cream, by intradermal injection of OVA and normal saline as the control, 25 mL each, on their abdomen skin.

2.2. Measurement of Epidermis Thickness and Data Analysis

OCT (OCM1300SS, Thorlabs Inc.), which is the imaging apparatus with 1325 nm bandwidth and 12 μm resolution capability, was used in this study. The hand probe was employed in the experiment to reduce the influence of the model animal's body motion. The probe was positioned upward direction, and guinea

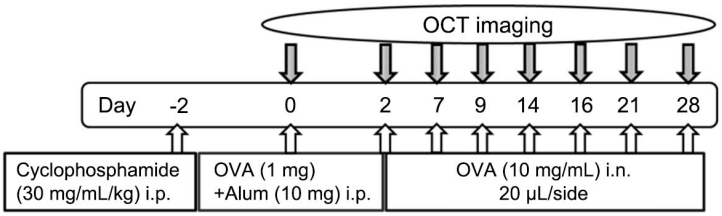

Figure 1. Experimental protocol of the allergic dermatitis-induced model.

pigs were put on it during the *in vivo* measurement; the models' body motion hardly influenced the measurement process.

A total of 400 2D-OCT images of 4.0 × 3.0 mm can be obtained in the single imaging process. We selected one in every 20 shots (0.15 mm interval) and measured the number of pixels of epidermis thickness at three locations in each selected image. As for the epidermis-dermis junction, we set the point with a radical inclination in the A-mode scan as the measurement standard.

The epidermis thickness on Day 9 was compared in the OVA administered site and control site by t-tests. The chronological changes in epidermis thickness were also compared by statistical analysis, using all statistical processing with a significance as $p = 0.05$.

3. *In Vivo* OCT Imaging of Abdomen Skin of the Guinea Pig

The intradermal injection was performed on Day 9, and the images of the OVA administered site and the normal saline administered site were captured at the timing when the allergen-induced flare reaction was confirmed on the OVA administered site. **Figure 2** shows the guinea pig's abdomen skin; (a) is the image immediately after the intraperitoneal administration and (b) shows the sites at the timing when allergic reactions were confirmed. In comparing (a) and (b), the flare reaction was evident at the OVA administered site, showing a swelling at the administered site, while little inflammation was observed at the control site, without any sign of swelling. **Figure 3** shows the OCT image of **Figure 2(b)**. The OVA administered site was indicated as (a), and the control site was indicated as (b). The part of epidermis and dermis were observed, and many black mottled sites were observed in (a). **Figure 4** shows the measurement results of epidermis thickness, which showed a significant increase at the OVA administered site. The average measurement read 42.3 μm at the OVA administered site and 23.1 μm at the control site, showing an evident thickening of the former with the reading of 1.8 times thicker than the latter.

As above, epidermis thickening was confirmed at the site with allergic reactions. When allergic dermatitis is induced, symptoms such as flare reaction or edema are commonly observed. Edemas should probably cause the epidermis thickening. In addition, the signal strength at the mottled sites shown in **Figure 3(a)** was low, suggesting them to be peripheral vessels [10]. The frequent appearances of the mottled sites showed a correlation with an inflammatory reaction, leading to the confirmation of allergic dermatitis development.

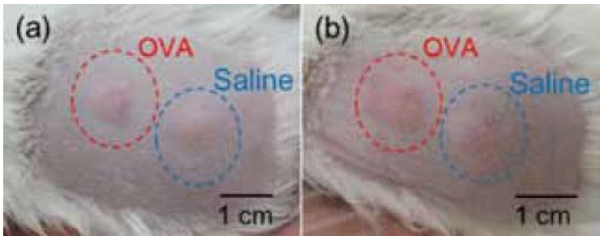

Figure 2. The photographic image of abdomen skin of the guinea pig. (a) Before an allergic reaction, (b) after showing an allergic reaction. OVA: the region of induced allergic dermatitis; Saline: control region.

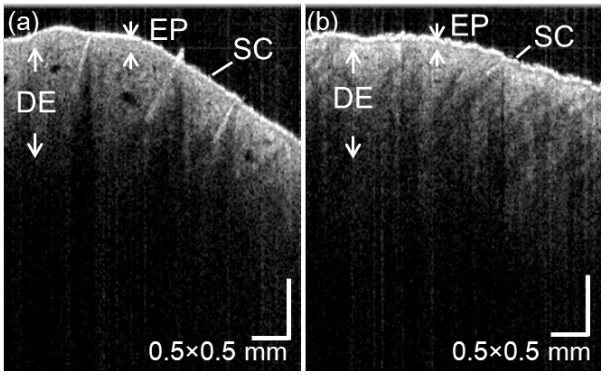

Figure 3. OCT image of abdomen skin of the guinea pig. (a) The region of induced allergic dermatitis, (b) control region. EP: epidermis; DE: dermis; SC: stratum corneum.

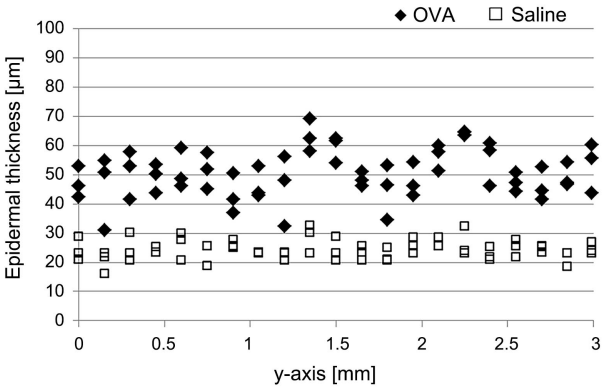

Figure 4. Comparison of epidermal thickness between the region induced allergic dermatitis and control region. OVA represents the region induced allergic dermatitis, Saline represents control region.

4. Daily Variations since the Onset of Allergic Dermatitis

Daily variations since the onset of allergic dermatitis were examined thoroughly. **Figure 5** shows the images of the guinea pigs' abdomen skin on (a) Day 0, (b) Day 7, (c) Day 14, and (d) Day 28, respectively. The allergic reaction was confirmed since Day 7, and the degree of flare reaction showed a steady increase according to the days passing. **Figure 6** shows the OCT image of inflammation

sites, namely, allergic reaction sites (a) to (d). As seen in the intracutaneous reaction, epidermis thickening became evident as the days passed since Day 7, and the capillary vessel expansion was confirmed since Day 14; the process of inflammation development was successfully observed. In addition, the scuffing of the surface skin became evident in the OCT images after Day 14. On the contrary, the control sites in Figure 6 did not show any sign of epidermis thickening nor capillary vessel expansion yet drying of the stratum corneum was observed since Day 14. Figure 7 shows the measurement results of epidermis thickness. Considering the reading at Day 0 as the reference point, the measurement results showed an evident epidermis thickening since Day 7, the allergic dermatitis onset date, and a steady increase in swelling according to the lapse of time; the measurement on Day 28 was twice as thick as that of the control.

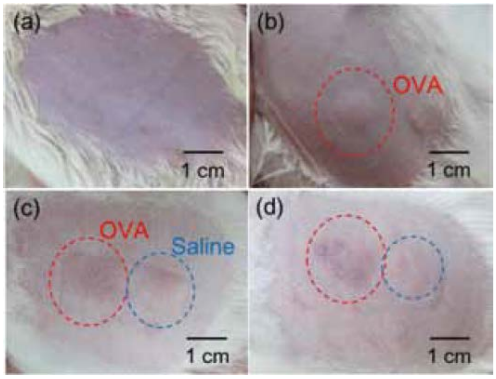

Figure 5. Images of the guinea pigs' abdomen skin at (a) Day 0, (b) Day 7, (c) Day 14, and (d) Day 28, respectively.

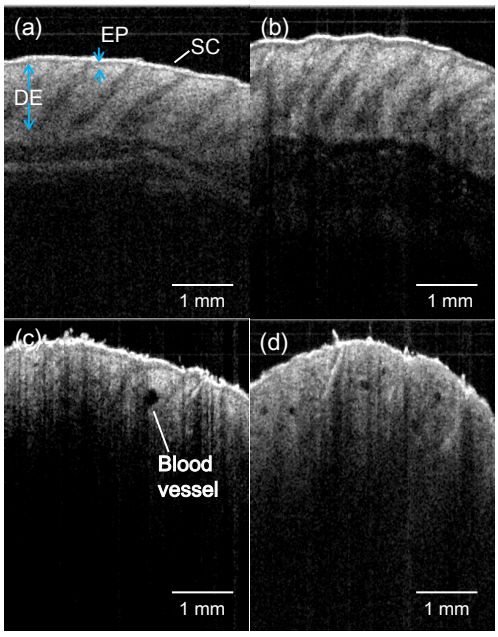

Figure 6. OCT image of inflammation sites, namely, allergic reaction sites (a) to (d).

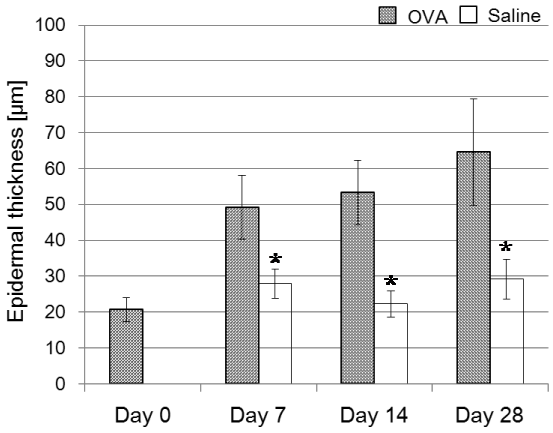

Figure 7. Experimental thickness between OVA and control (*) from Day 0 to Day 28.

5. Discussion and Conclusions

We have successfully performed a series of microscopic observations on the inflammatory process of allergic dermatitis using OCT. Epidermal swelling and capillary vessel expansion were observed at the inflammation sites, and epidermal thickness was 1.8 times as thick as that of the control. In addition, chronological observation showed allergic symptoms since Day 7, and the epidermal thickening became more evident according to the days passed. After Day 14, intradermal capillary vessels began to show evident expansion, indicating a confirmed inflammation.

The amount of transepidermal water loss (TEWL) is significantly larger in patients with allergic dermatitis than the healthy subjects, whether at a lesion part or non-lesion part is irrelevant [12] [13]. Therefore, TWL influence was a possible reason for the roughness on the skin surface, as shown in **Figure 6** being observed in the control sites after Day 14. It is also possible that capturing sufficient OCT images in the depth direction was challenging because the signal strength was weakened by the OCT light being scattered or reflected from the roughness of the skin surface as well as from the moisture level increase on the skin surface due to the fluid discharge from edema.

In this study, OCT is powerful tool for *in vivo* observation of the animal model with allergic dermatitis developed by chemical administration to examining their skin inflammation. The results expected in this study would provide valuable information regarding structural/histological alteration in the skin during the development process of dermatitis.

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Ethical Concerns

This study was conducted under approval from the ethics review board of the Animal Care and Use Committee for Osaka University Graduate School of Medicine (No. 29-02-01).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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