Acrosyringium Is the Main Site of the Vesicle/Pustule Formation in Palmoplantar Pustulosis

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Pustulosis palmaris et plantaris or palmoplantar pustulosis (PPP) is a refractory pustular eruption on the palms and soles with unknown etiology. Numerous eccrine sweat pores exist on the palms and soles, suggesting the involvement of eccrine sweating in the pathogenesis of PPP. To the best of our knowledge, however, no definite abnormality in sweating has been documented in PPP. Accordingly, we analyzed the eccrine sweat duct involvement in the mechanism of vesicle formation in PPP. Dermatoscopy showed that PPP vesicles are located on the top of the ridges but not in the furrows. The sweat secretion in the lesional area was much lower than that in the nonlesional area, with or without pain stimulation to induce sweating. Immunostaining of horizontal sections of the lesions using antibodies against gross cystic disease fluid protein-15 (GCDFP-15) and epithelial membrane antigen (EMA) showed that these markers were localized in the cells lining the intraepidermal vesicles. Although the sweat antimicrobial peptides, dermcidin and human cathelicidin antimicrobial peptide 18 (hCAP-18)/LL-37, were detected in the fluid of the vesicles/pustules, neither dermcidin nor hCAP-18/LL-37 were overexpressed by neighboring keratinocytes. These findings suggest that the acrosyringium may be involved as the main site of the vesicle formation in the pathomechanism of PPP.

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INTRODUCTION

Pustulosis palmaris et plantaris or palmoplantar pustulosis (PPP) is a chronic pustular dermatitis characterized by palmoplantar intraepidermal vesicles filled with neutrophils (Uehara and Ofuji, 1974). Although it is a common skin disease often recalcitrant to available treatments, the pathogenesis remains unknown. Numerous eccrine sweat pores exist on the palms and soles, and several reports suggest the involvement of eccrine sweating in the pathogenesis of PPP (Krieg *et al.*, 1992; Eriksson *et al.*, 1998). To the best of our knowledge, however, no definite abnormality in sweating has been documented in PPP.

The eccrine sweat gland is a secretory as well as an excretory organ. Although the sole function of sweat has been considered to be thermoregulation during exposure to a hot environment or during physical exercise, recent evidence indicates that it has a role in the innate immune response. Previously, two major classes of antimicrobial peptides were identified in mammalian skin: cathelicidins (Zanetti *et al.*, 1995; Gallo *et al.*, 1997; Nizet *et al.*, 2001) and β-defensins (Harder *et al.*, 1997; Stolzenberg *et al.*, 1997; Ali *et al.*, 2001). Cathelicidins, which are similar to many other antimicrobial peptides, are synthesized as a preproprotein (Zanetti *et al.*, 1995). The only cathelicidin in humans is human cathelicidin antimicrobial peptide (hCAP-18)/LL-37 (Agerberth *et al.*, 1995; Frohm *et al.*, 1997) and it is expressed in leukocytes as well as on a variety of epithelial surfaces. The hCAP-18/LL-37 has been detected in human skin keratinocytes, but only at the site of inflammation, suggesting that this antimicrobial peptide functions primarily in response to injury rather than modulating colonization of the skin's surface (Frohm *et al.*, 1997). Another antimicrobial peptide, dermcidin, was recently detected in the human sweat gland, suggesting that sweat may have an additional important role in protection against various bacteria (Schittek *et al.*, 2001). Recently, we have shown the expression of hCAP-18/LL-37 in eccrine sweat glands (Murakami *et al.*, 2002), which confirms the role of antimicrobial peptides in protecting the body surface through innate immunity.

To dissect the involvement of the eccrine sweat duct in the pathomechanism of vesicle formation in PPP, a possible abnormality in the process of sweating was analyzed in early lesions of PPP. Because the vesicle formation can be rapidly induced by infection, stress, and so on, it is plausible to speculate that the preexisting acrosyringium is involved in the formation of the lesion. Our data provide a support for the hypothesis that an abnormality in sweating initiates the

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Abbreviations: EMA, epithelial membrane antigen; GCDFP, gross cystic disease fluid protein; hCAP, human cathelicidin antimicrobial peptide; PBS, phosphate-buffered saline; PMN, polymorphonuclear neutrophils; PPP, palmoplantar pustulosis; RT, room temperature; TTBS, Tween Tris-buffered saline

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formation of vesicles, suggesting a pathophysiological mechanism for PPP.

RESULTS

PPP vesicles were located on the ridges of palmar skin

Dermatoscopy clearly showed that small vesicles and vesicopustules were located in a linear manner on the top of the ridges but not in the furrows of the palmar skin (Figure 1). Some large vesicles or pustules extended into the furrows.

Sweat secretion in the lesional area was decreased compared with that in the nonlesional area

Sweat secretion was compared between the lesional and nonlesional areas of the palmar skin. At the time of measurement, the patient's palm showed several small vesicles with a few pustules. Sweat volume in the lesional area (B) was much lower than that in the non-lesional area (A) or the contralateral healthy palm(s) (Figure 2). The sweat volume in the nonlesional area was increased after pain stimulation, whereas that in the lesional area remained low.

Small vesicles were located in/and around the epidermal sweat ducts in the early lesions

PPP vesicles were located within the epidermis, with typical pustule formation (Figure 3). Keratinous material in the acrosyringium was also observed (Figure 3a). A small vesicle related to acrosyringium could be observed in the epidermis (Figure 3b). The vesicle turned into a tiny pustule filled with small round cells and neutrophils (Figure 3c). Microabscess formation was observed in the epidermis with remarkable inflammatory cell infiltration around the pustule (Figure 3d). Finally, the lesion resolved to normal-appearing epidermis (Figure 3e). Using horizontal sections, immunostaining with gross cystic disease fluid protein 15 (GCDFP-15) and epithelial membrane antigen (EMA) showed that these signals were localized to the acrosyringium showing pores in the

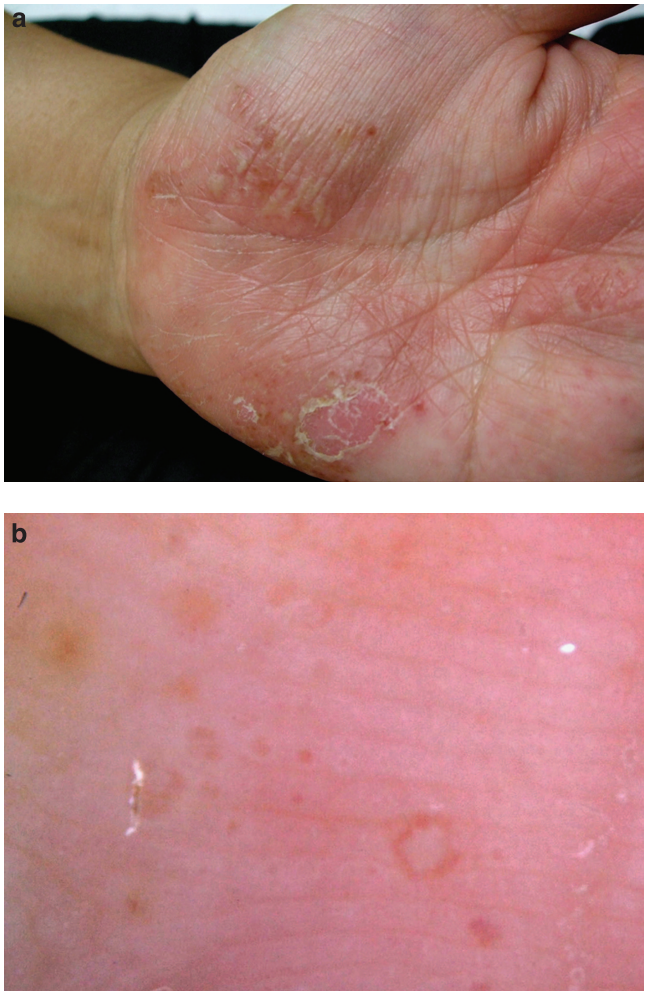

Figure 1. Dermatoscopic findings of the palm of palmoplantar pustulosis (PPP). (**a**) The palm of the patient with PPP shows small vesicles, small pustules, desquamation, and erythema. (**b**) Dermatoscopy shows that many vesicles of various sizes are located on the top of the ridge together with large pustules.

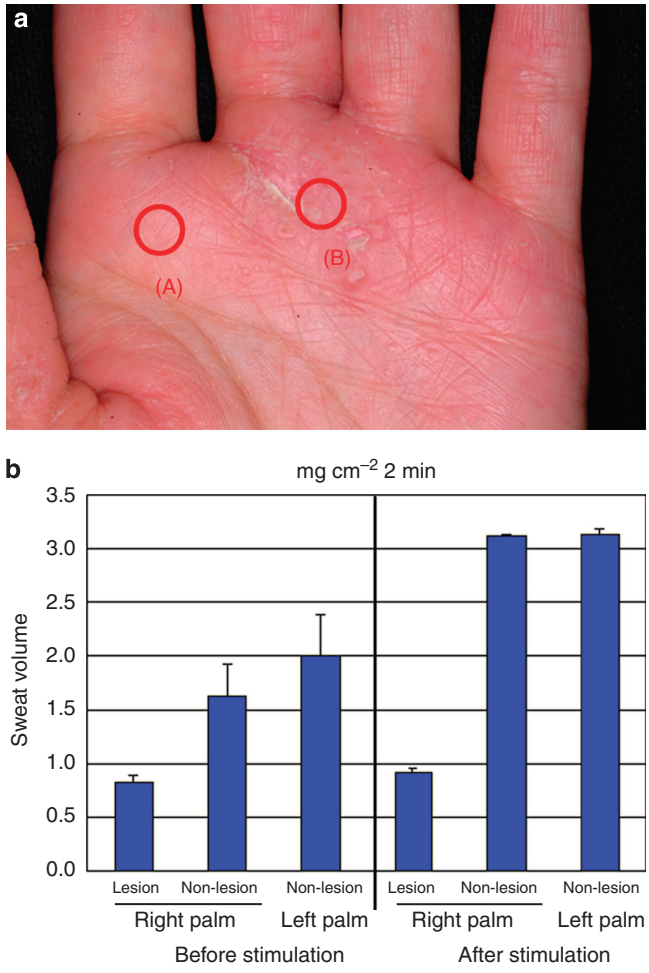

Figure 2. Lesional area shows decreased sweating compared with the nonlesional area. (**a**)The 2-minute sweat volume was measured from the nonlesional (A) and lesional area of palmoplantar pustulosis (PPP) (B) as well as from a healthy palm. Basal sweat secretion of the lesional area was much lower than that of the nonlesional area and of the healthy palms ($P<0.05$). After pain stimulation, sweat secretion was increased significantly in the nonlesional area and the other healthy palm (**b**) but not in the lesional area.