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ORIGINAL PAPER

Prurigo nodularis as a sweat gland/duct-related disorder: resolution associated with restoration of sweating disturbance

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Abstract

Little attention has been given to the involvement of sweat glands/ducts in the pathogenesis of prurigo nodularis (PN). According to recent studies, PN is likely to develop under conditions characterized by dry skin, such as atopic dermatitis (AD), suggesting a strong impact of skin dryness on PN development. No therapeutic modalities produced complete resolution of PN without exacerbations. We previously reported that increases in skin dryness by sweating disturbance could initiate the development of AD. We investigated whether sweating responses were impaired in refractory PN lesions; and, if so, we asked whether the PN lesions could resolve by restoring sweating disturbance. Using the impression mold technique, which allows an accurate quantification of individual sweat gland/duct activity, we examined basal sweating under quiescent conditions and inducible sweating responses to thermal stimulus in PN lesions and normal-appearing skin in the same patients before and after treatment with a moisturizer or topical corticosteroids. Sweating disturbance, either basal or inducible, was most profoundly detected in the "hub" structure corresponding to the center of PN papule before the treatment. This sweating disturbance was immunohistochemically associated with the leakage of sweat into the dermis. This disturbance was restored by treatment with a moisturizer. Our limitations include a relatively small patient cohort and lack of blinding. Sweating disturbance could be one of the aggravating factors of PN development. Refractory PN with low skin hydration may resolve by restoring sweating disturbance.

Keywords Prurigo nodularis · Sweating disturbance · Leakage of sweat

Abbreviations

AD	Atopic dermatitis
DCD	Dermcidin
HC	Healthy controls
IMT	Impression mold technique
LA	Lichen amyloidosis
LP	Lichen planus
PN	Prurigo nodularis

Introduction

Prurigo nodularis (PN) lesions tend to show a predilection to the extensor surfaces of the upper and lower limbs and flexural areas are usually spared [1, 3, 7, 8]. A recent trend in English literature suggests the importance of considering neural sensitization to itch and neurogenic inflammation as primary components initiating and maintaining chronic pruritus in PN lesions [2, 6, 9, 14]. Nevertheless, the finding that water content of skin in extensor surfaces of the limbs is significantly lower than that in flexural areas [10, 11] suggest that skin dryness may have a strong impact on the development of PN. Indeed, PN has been reported to develop in 65–80% of atopic dermatitis (AD) cases [13], in which dry skin is the hallmark. We have recently demonstrated that increases in skin dryness by sweating disturbance could initiate the development of AD [11] and lichen amyloidosis (LA) [10]. To qualify sweating disturbance, we have recently established a useful method, named the impression mold technique (IMT), which allows an accurate quantification of individual sweat gland/duct activity

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delivering sweat in a well-defined location [10, 11]. We, therefore, asked whether sweating disturbance could be detected in PN lesions, and if so, we next asked whether PN lesions refractory to various therapies could resolve by restoring the sweating disturbance.

Methods

Patient characteristics and trial design

Twenty-seven patients (mean age, 51 years, 9 males and 18 females), who visited our hospital for severe PN unresponsive to topical corticosteroids between 2015 and 2017, were screened for eligibility. The study was approved by the Institutional Review Board at Kawasaki Medical University and followed the guidelines for the ethical conduct of human research. Of these patients, 18 patients (mean age, 44 years; range, 11–84 years) were selected if they had more than six symmetrical PN papules/nodules on their extremities, which had persisted for at least 1 month before the initial presentation. All patients gave written informed consent. Safety was assessed by recording adverse events at all visits by two dermatologists (YA and CK). If participants exhibited any symptoms suggestive of adverse events, they were immediately removed from the study and treated appropriately. Fortunately, however, no participants discontinued the trial due to adverse events. In addition, patients were included only if sweating responses were examined both before start of therapy and after therapy.

The participants were treated with clobetasol propionate 0.05% ointment and 0.3% heparinoid. A maximum application of one or three finger-tip-unit (1FTU or 3FTU) for clobetasol propionate and heparinoid, respectively, for each area twice daily, morning and evening. All participants were requested to apply these agents at almost same time (7–9 am and 5–8 pm), to exclude any influence of circadian rhythm. The amount of topical agent used as 3FTU was 18 mg/cm^2. Heparinoid cream is a medical cream, Hirudoid^R cream (Maruho Pharmaceutical, Japan) have been available in Asian countries, which is an oil-in-water emulsion containing 0.3% heparinoid, propylene glycol, hard paraffin, sodium lactate, cetostearyl alcohol, and purified water. The participants were instructed to apply either a moisturizer, corticosteroids allocated on the identified area for 4 weeks.

The characteristics of 13 patients completed 4 weeks of topical therapy followed by sweating observation are shown in Table 1, while the other five patients were eventually excluded due to loss of compliance and follow-up after the first visit, but none due to adverse events. Most patients

Table 1 Patient characteristics

Case	Age (years)	Sex	Site	Duration (years)	Topical steroids used in previous treatment	Comorbidities	Treatment	Outcome
1	24	M	Forearm, trunk	23.0	Class 1	AD	Moisturizer	PR
2	68	F	Forearm, thigh	0.2	Class 2	Hyperlipidemia	Moisturizer	PR
3	29	F	Forearm, lower legs, thigh	8.0	Class 1	AD	Moisturizer Clobetasol propionate	CR PR
4	34	F	Forearm, lower legs, thigh, trunk	0.4	Class 2	AD	Moisturizer Clobetasol propionate	CR CR
5	11	F	Thigh, buttock	0.1	Class 1	None	Moisturizer Clobetasol propionate	CR PD
6	25	F	Forearm, lower legs	20.0	Class 1 and 2	AD	Moisturizer Clobetasol propionate	CR NR
7	34	F	Lower legs	1.5	Class 2	AD	Moisturizer	PR
8	37	F	Upper arm, forearm, thigh	0.3	Class 2	None	Moisturizer	PR
9	42	F	Thigh	2.0	Class 1	None	Moisturizer	PR
10	43	M	Forearm	34.0	Class 1	Asthma	Moisturizer Clobetasol propionate	NR NR
11	46	F	Forearm	0.2	Class 2	None	Mixture of topical steroids and moisturizer	PR
12	64	M	Thigh	3.0	Class 1 and 2	Diabetes	Mixture of topical steroids and moisturizer Clobetasol propionate	PR NR
13	72	M	Lower legs	10.0	Class 1 and 2	Diabetes	Moisturizer Clobetasol propionate	CR NR

AD atopic dermatitis, *CR* complete response, *F* female, *M* male, *NR* no response, *PD* progressive disease, *PR* partial response

were instructed to apply each topical agent at either right or left side, twice a day. Six patients of these 13 patients were treated with the moisturizer alone on the one side, or clobetasol propionate 0.05% ointment on the opposite side. Another two patients were treated with a heparinoid moisturizer in combination with topical corticosteroids and five patients were treated with a heparinoid moisturizer alone. Responses to treatment were categorized as complete response (complete resolution of the lesions, CR), partial response (at least a 50% reduction in PN lesions, PR), no response (< 50% reduction in PN lesions, NP) and progressive disease (worsening in PN lesions, PD) in the application site. The response to therapy was documented at 4 weeks and at subsequent visits in comparison with the severity of PN lesions at baseline.

Evaluation of basal and inducible sweating responses in PN lesions

In all patients, sweating responses were evaluated under quiescent conditions (basal sweating) and 15–30 min after thermal stimulus (inducible sweating) by the IMT [9, 10]. The measurement was performed in an air-conditioned room (room temperature, 22–24; and relative humidity (RH), 40–50%) and all participants were allowed to acclimate to the temperature for at least 20 min prior to the test.

The structure of each PN papule/nodule was defined as hub, periphery and uninvolved areas, as shown in Fig. 1a. Using the IMT, sweat droplets were visualized as small holes corresponding to sweat pores (Fig. 1b). Diameter and size of the sweat droplets were analyzed by digital microscope (VHX-5000, Keyence). The sweat response to thermal stimulus was induced by immersion of both legs to knee level for 30 min in a water bath maintained at 43 °C, as previously described [10, 11].

Results

Basal and inducible sweating responses

We investigated whether sweating responses under quiescent conditions (basal sweating) and after thermal stimulus (inducible sweating) could be impaired in lesional and normal-appearing skin of typical PN patients before treatment in patients. As shown in Fig. 1b–d, under quiescent conditions (0 min), a profound decrease in the mean number of sweat droplets was found in the hub, as demonstrated in our previous study on LA papules [10]. Fifteen–thirty minutes after thermal stimulus, few sweat droplets became visible even at the hub but the number and diameter of sweat droplets were decreased at the hub, periphery and uninvolved skin than those in the forearm of healthy controls and normal-appearing skin of the same patients (Fig. 1b–d). Nevertheless, in normal-appearing skin from the same patients, basal and inducible sweating responses were not different from those in healthy controls, indicating that sweating disturbance detected by IMT could be limited to the PN lesions. In other words, PN could preferentially develop in areas with sweating disturbance.

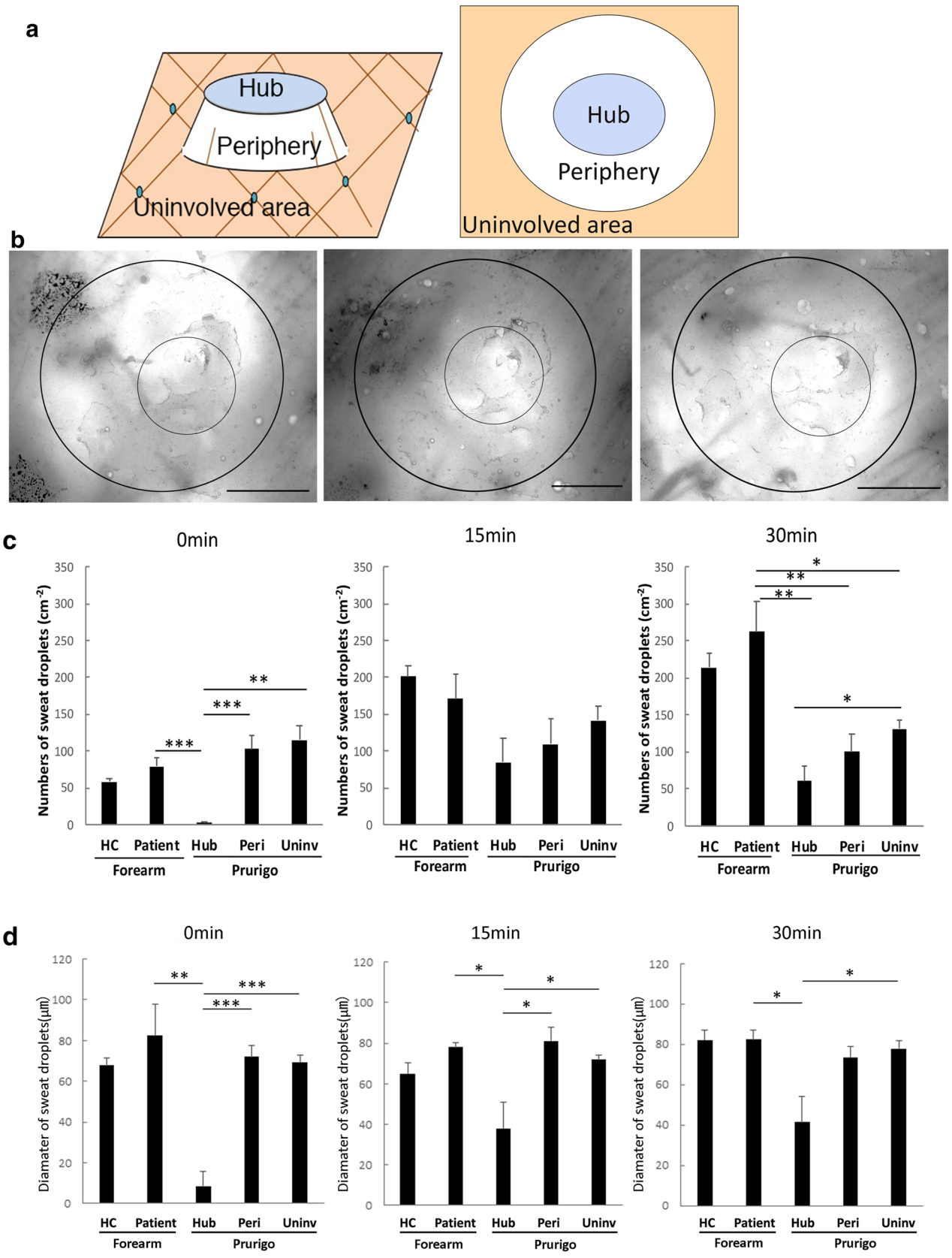
Restoration of sweating disturbance after treatment with a moisturizer

We then asked whether resolution of PN lesions by treatment with a moisturizer or topical corticosteroids could be associated with restoration of sweating disturbance. We compared basal and inducible sweating responses in PN lesions before and after 4-week treatment. As shown in Fig. 2 after treatment with a moisturizer, sweating disturbance, either basal or inducible, was restored to the levels indistinguishable from those in normal-appearing skin of the PN patients and healthy controls.

In the PN lesions resolved by 4-week treatment with a moisturizer, a marked increase in basal sweating was detected, especially when 3FTU of a moisturizer was used, coincident with restoration of fine skin surface structures composed of dermal folds and ridges (Fig. 3a). In contrast, in the PN lesions treated with clobetasol propionate, not only basal sweating but also inducible sweating remained defective and the skin surface structures remained disturbed, even when 3FTU of clobetasol was used, despite slight flattening of the lesions (Fig. 3b). Importantly, restoration of basal sweating responses occurring coincident with the appearance of skin surface structures could be interpreted as suggesting that maintaining basal sweating responses is prerequisite for the resurgence of the skin surface structure. These results suggest that clinical resolution of the PN lesions by a moisturizer is associated with the restoration of sweating responses. As shown in Table 2, in four patients the moisturizer-treated site showed CR.

Leakage of sweat in the evolved PN lesions

We next investigated whether leakage of sweat could be also immunohistochemically identified in the PN lesions after thermal stimulus, as shown in LA [10]. As shown in Fig. 4a, b, dermcidin (DCD), one of sweat-specific components, was immunohistochemically detected not only within the sweat glands/ducts but also in the dermis adjacent to the sweat glands/ducts either in the PN lesions 30 min after thermal stimulus. These results suggest that sweating disturbance detected in the PN lesions could be due in part to leakage of sweat, but not due to the portal occlusion.


a
Hub
Periphery
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c
0min
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Numbers of sweat droplets (cm-2)
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Diamater of sweat droplets(μm)
HC Patient Hub Peri Uninv
Forearm
Prurigo

◂**Fig. 1** Schematic models, representative silastic molds and mean number and diameter of sweat droplets in healthy controls (HC) and prurigo nodularis (PN) patients before (basal sweating) and after thermal stimulus (inducible sweating) at baseline. **a** Schematic PN model composed of a flat-topped central area devoid of skin folds ("hub") and structures surrounded by radial streaks ("periphery"). **b** Representative silastic molds from PN lesions (case 1). Silastic impression molds were obtained from non-treated PN lesion under quiescent conditions and after thermal stimulus, labeled as 0 min, 15 min and 30 min, respectively. Note the complete absence of sweat droplets in the hub either before or after thermal stimulus. A few sweat droplets are observed in the peripheral area and uninvolved areas after thermal stimulus. Bar = 1 mm. Graphically illustrated are the mean number (**c**) and diameter (**d**) of sweat droplets at normal-appearing skin in the forearm in HC ($n=7$) and PN patients ($n=13$), and those at the hub, periphery and uninvolved area of non-treated PN lesion in patients. *HC* healthy controls, *Hub* hub, *Peri* periphery, *Uninv* uninvolved area of PN lesions. *P* values labeled as $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ were determined by Student *t* test

Discussion

We have demonstrated that PN lesions, particularly the center "hub", have a pronounced defect in basal and inducible sweating responses in a site-restricted manner. Although we also demonstrated similar sweating defects in other inflammatory skin diseases such as AD, lichen planus (LP), and LA, each skin disease could display its own unique pattern of sweating defects: sweating defects in LP and LA [5, 10–12], are characterized by a pronounced defect in the center "hub" not associated with compensatory hyperhidrosis in the periphery, while those in AD are associated with compensatory hyperhidrosis in the periphery and could progress involving all of the body which eventually result in systemic hypohidrosis [11]: in AD, sweating responses are progressively impaired with the development of the disease. In PN lesions, compensatory hyperhidrosis was only detected in basal, but not inducible, sweating at the periphery, unlike AD, in which compensatory hyperhidrosis was detected both in basal and inducible sweating responses at the early stage. In this regard, LP and LA papules appear to remain confined to the lesional skin, while AD and PN lesions have the tendency to spread to peripheral involvement. The cause of sweat leakage in PN is unclear; however, it may be related to the reduced expression of claudin-3, the major component of tight junctions in sweat glands, in AD lesional skin [15]: decreased claudin 3 expression in AD lesional skin has been shown to be associated with sweat leakage. This finding could explain why patients who develops PN at a younger age are more likely to have an atopic diathesis [1, 3, 13].

One may argue that sweating disturbance demonstrated here might simply be the consequence of inflammation, hyperkeratosis and tissue damage and thus not serve a true pathological role. In support of the pathogenic role, however, sweating disturbance was detected even in early PN lesions characterized by less firm and less infiltrated papules resembling prurigo simplex subacuta, as well as those in fully evolved PN lesions with marked acanthosis and hyperkeratosis (data not shown). In addition, the resolution of PN lesions refractory to various treatment modalities was only observed by restoring the sweating disturbance with the use of a moisturizer. These findings suggest that sweating disturbance may thus be involved in an early step in the development of PN lesions, but not a second or late event with limited contributions to disease expression in the skin. If so, leakage of sweat into the dermis could represent one of the early events which could result in a decrease in the sweat delivery to the skin surface, unexplained itching and strange sensation [11], and activation of inflammatory cells in the dermis.

Topical corticosteroids have long been regarded as a first-line therapy for PN. Because of their atrophogenic properties and a gradual loss of the therapeutic efficacy, however, the long-term use of topical corticosteroids should be somewhat limited. In this regard, our findings suggest that topical corticosteroids impair both basal and inducible sweating responses, as shown in Fig. 2. In addition to their inhibitory effect on sweating responses, topical corticosteroids may cause acute folliculitis with bacteria and/or yeast, which may in turn give rise to the new PN lesions. These results can be interpreted as suggesting the possibility that a gradual loss of therapeutic efficacy of topical corticosteroids for PN may be caused by decreased sweating responses. In support of this possibility, a previous observation suggested that repeated applications of topical corticosteroids may cause sweat gland/duct fragility as a result of downregulation of tight junction proteins [4], thereby providing a mechanism for leakage of sweat into the dermis.

If PN papules/nodules were surrounded by dry skin, one could expect that these PN lesions may have been triggered by leakage of sweat into the dermis. The development of refractory PN in the corticosteroid-treated site could be an unintended consequence of topical corticosteroids. Thus, therapies for refractory PN could be primarily directed at restoring sweating disturbance. Moisturizers seem to be another option for refractory PN treatment with their efficacy for sweating disturbance but the role of corticosteroids in PN management needs to be further investigated.

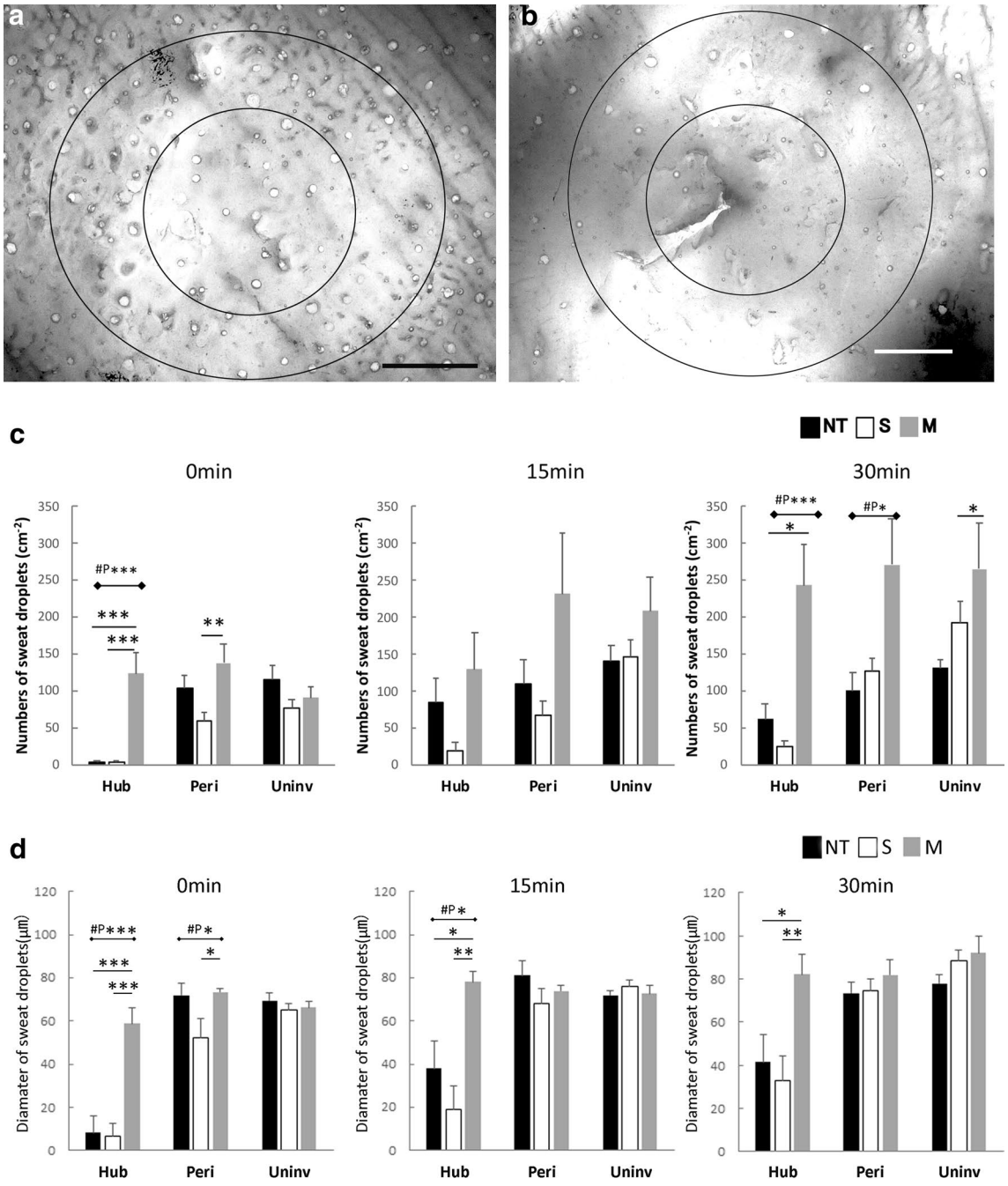

Fig. 2 Representative silastic molds from the lesions of a patient (case 3) after treatment with a moisturizer or clobetasol propionate (3FTU) after thermal stimulus, labeled as 15 min (**a**, **b**) and mean number and diameter of sweat droplets in treated prurigo nodularis (PN) after thermal stimulus (inducible sweating). Note that the increase in the number of sweat droplets at the hub area was detected after treatment with a moisturizer (**a**). Numbers of sweat droplets are increased in the periphery and uninvolved area at the moisturizer-treated site (**a**) as compared with those at the clobetasol propionate-treated site (**b**), after thermal stimulus. *CR* completely response, *PR* partial response. Bar = 1 mm. The mean number (**c**) and diameter (**d**) of sweat droplets at the hub, periphery and uninvolved area of the PN lesions not treated (NT), or treated with clobetasol propionate ($n = 7$, S) or a moisturizer ($n = 11$, M). *Hub* hub, *M* moisturizer, *Peri* periphery, *S* clobetasol propionate, *Uninv* uninvolved area of PN lesions. *P* values labeled as $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ were determined by Student *t* test. *P* values labeled as *#P* were determined by ANOVA

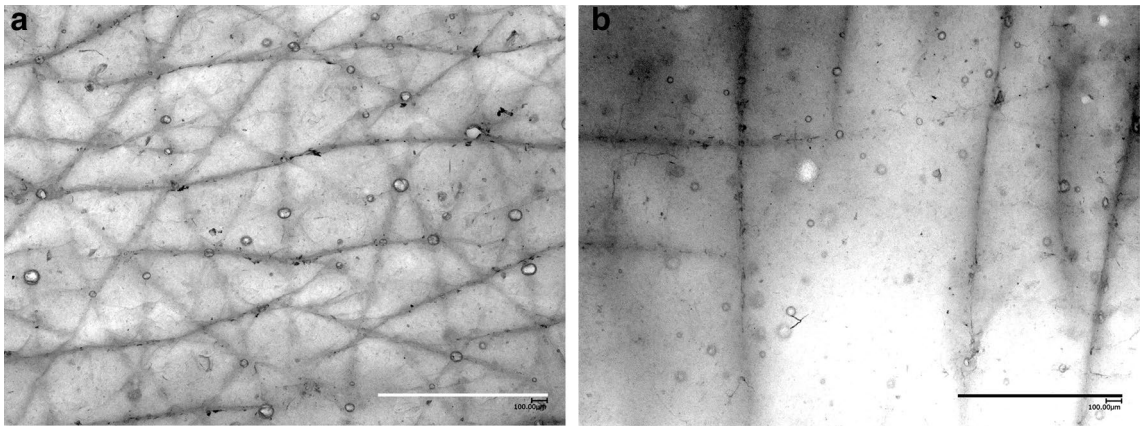

Fig. 3 Prurigo nodularis (PN) treated with a moisturizer or clobetasol propionate (3FTU). Representative silastic molds of lesions (**a**, **b**) in case 4. Silastic impression molds were obtained from completely resolved (CR) lesion treated with a moisturizer (**a**) and CP (**b**) under quiescent conditions. Note the complete recovery of skin folds and the increase in the sweat droplet number in the moisturizer-treated hub area. In contrast, in the CP-treated area only a few sweat droplets and no folds are observed. Red and black open circles represent sweat droplets at the skin ridge and skin fold, respectively. *CR* complete response. Bar = 1 mm

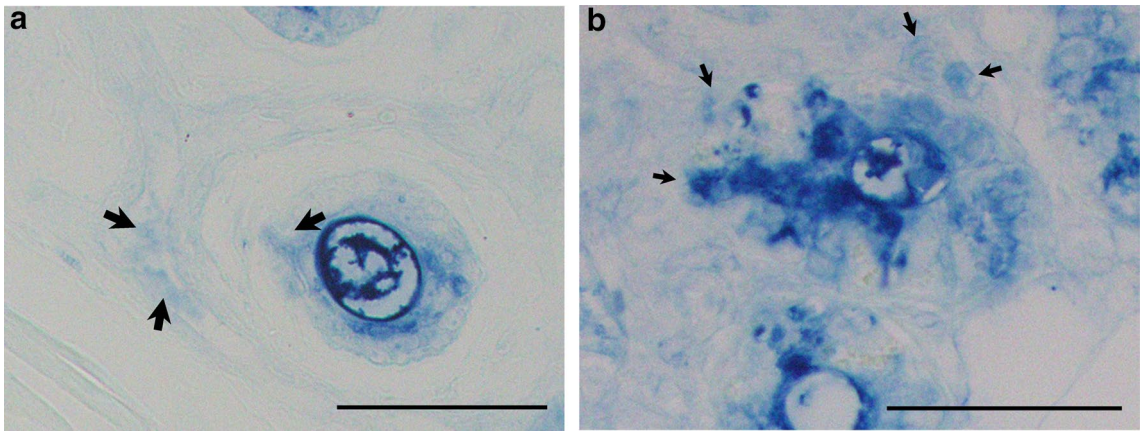

Fig. 4 Prurigo nodularis (PN). Immunohistochemical detection of sweat leakage around sweat ducts and sweat glands in non-treated lesions. Staining for dermcidin (DCD; blue), for nuclear staining (nuclear fast red; pink). Leakage of DCD around the sweat ducts (**a**) and sweat gland (**b**) (indicated by arrows) is detected at non-treated PN at 30 min after thermal stimulus in cases 1 (**a**) and 2 (**b**). Bar = 50 μm

Table 2 Clinical response for topical therapies

	CR	PR	NR + PD
Moisturizer ($n = 11$)*	4	6	1
Clobetasol propionate ($n = 7$)	1	1	5

CR complete response, *NR* no response, *PD* progressive disease, *PR* partial response

*$P = 0.038$ was determined by Fisher's exact test

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institutional Review Board at Kawasaki Medical University and followed the guidelines for the ethical conduct of human research (2238-4).

References

1. Jorizzo JL, Gatti S, Smith EB (1981) Prurigo: a clinical review. J Am Acad Dermatol 4(6):723–728
2. Kitagaki H, Hiyama H, Kitazawa T, Shiohara T (2014) Psychological stress with long-standing allergic dermatitis causes

psychodermatological conditions in mice. J Invest Dermatol 134(6):1561–1569. https://doi.org/10.1038/jid.2014.31
3. Lee MR, Shumack S (2005) Prurigo nodularis: a review. Australas J Dermatol 46(4):211–18–quiz219–20. https://doi.org/10.1111/j.1440-0960.2005.00187.x
4. Lee SE, Choi Y, Kim S-E et al (2013) Differential effects of topical corticosteroid and calcineurin inhibitor on the epidermal tight junction. Exp Dermatol 22:59–61
5. Mizukawa Y, Yamazaki Y, Shiohara T (2019) Leakage of sweat into the dermo-epidermal junction as a possible trigger for lichen planus lesion development. Arch Dermatol Res 311(1):71–82
6. Paus R, Schmelz M, Bíró T, Steinhoff M (2006) Frontiers in pruritus research: scratching the brain for more effective itch therapy. J Clin Invest 116(5):1174–1186. https://doi.org/10.1172/JCI28553
7. Rowland Payne CM, Wilkinson JD, McKee PH, Jurecka W, Black MM (1985) Nodular prurigo–a clinicopathological study of 46 patients. Br J Dermatol 113(4):431–439
8. Saco M, Cohen G (2015) Prurigo nodularis: picking the right treatment. J Fam Pract 64(4):221–226
9. Schmelz M (2010) Itch and pain. Neurosci Biobehav Rev 34(2):171–176. https://doi.org/10.1016/j.neubiorev.2008.12.004
10. Shimoda Y, Sato Y, Hayashida Y et al (2017) Lichen amyloidosis as a sweat gland/duct-related disorder: resolution associated with restoration of sweating disturbance. Br J Dermatol 176(5):1308–1315. https://doi.org/10.1111/bjd.15060
11. Shimoda-Komatsu Y, Sato Y, Yamazaki Y, Takahashi R, Shiohara T (2018) A novel method to assess the potential role of sweating abnormalities in the pathogenesis of atopic dermatitis. Exp Dermatol 27(4):386–392. https://doi.org/10.1111/exd.13448
12. Shiohara T, Sato Y, Komatsu Y, Ushigome Y, Mizukawa Y (2016) Sweat as an efficient natural moisturizer. Curr Probl Dermatol 51:30–41. https://doi.org/10.1159/000446756
13. Tanaka M, Aiba S, Matsumura N, Aoyama H, Tagami H (1995) Prurigo nodularis consists of two distinct forms: early-onset atopic and late-onset non-atopic. Dermatology 190(4):269–276
14. Tey HL, Yosipovitch G (2011) Targeted treatment of pruritus: a look into the future. Br J Dermatol 165(1):5–17. https://doi.org/10.1111/j.1365-2133.2011.10217.x
15. Yamaga K, Murota H, Tamura A et al (2018) Claudin-3 loss causes leakage of sweat from the sweat gland to contribute to the pathogenesis of atopic dermatitis. J Invest Dermatol 138(6):1279–1287