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Invited Review Article

Dry skin manifestations in Sjögren syndrome and atopic dermatitis related to aberrant sudomotor function in inflammatory allergic skin diseases^{*}

Ichiro Katayama

Department of Dermatology, Course of Integrated Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamada-oka, Suita-shi, Osaka 565-0871, Japan

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ABSTRACT

We have reported characteristic cutaneous manifestations of Sjögren syndrome (SS) with special references to autoimmune anhidrosis or hypoidrosis and related mucocutaneous manifestations in addition to annular erythema or cutaneous vasculitis. Although significance of cutaneous manifestations of SS has been gradually recognized in rheumatologists, sudomotor function has not been fully evaluated and recognized in the diagnosis of SS except for dermatologists. SS is a relatively underestimated collagen disease in contrast to SLE, systemic sclerosis, or dermatomyositis, special care should be needed not to make misdiagnosis of SS when we see the patients with common skin disease such as, drug eruption, infections skin disease or xerosis in the daily practice. In contrast to pathomechanisms of dry skin observed in SS, we recently reported that reduced sweating function and dry skin seen in atopic dermatitis (AD) are mediated by histamine or substance P, those are usually restored to normal levels after improvement of the dermatitis by topical corticosteroid ointment with or without oral anti-histamine. Therefore, xerotic skin lesions seen in SS and AD might be attributable to different pathomechanisms with similar dry skin manifestations. We recently reported that SS promotes dry skin when complicated with AD possibly due to acceleration of hypoidrosis. In this review, we would like to summarize our recent understanding of regulatory mechanism of impaired sweating function in allergic inflammatory skin diseases by introducing clinical presentations of AD/SS overlap cases as the model of hypoidrotic inflammatory skin diseases.

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Introduction

Sjögren syndrome (SS) was first reported by Swedish ophthalmologist, Henrik Sjögren in 1930 as a case of keratoconjunctivitis sicca associated with rheumatoid arthritis. Since then, clinical, etiological and epidemiological analyses have been conducted in the world and now SS is recognized as autoimmune epithelitis or autoimmune sialoadenitis induced by autoreactive T cells or tissue specific autoantibodies. The SS patients develop various types of exocrine manifestations such as autoimmune thyroiditis, interstitial nephritis, or pneumonitis during the clinical course. B cell

lymphoma/pseudo lymphoma or several types of skin diseases are known as extraglandular manifestations of SS.

Known mucocutaneous manifestations associated with SS include hypoidrosis-related skin dryness and blepharitis or angular cheilitis as glandular manifestations, and hypergammaglobulinaemic purpura or urticarial vasculitis as extraglandular manifestations. In addition to these skin lesions, we have previously reported that Japanese SS patients occasionally develop annular erythema (AE) with perivascular and periappendageal lymphocytic infiltration, which is characterized by a wide elevated border and central pallor.^{1,2} As only a few cases of AE in SS have been reported in Caucasians,^{3,4} and because AE in Japanese SS patients shares many features with subacute cutaneous lupus erythematosus (SCLE), the most photosensitive type of lupus erythematosus (LE),⁵ SS manifesting with AE has been thought to be the Oriental counterpart of SCLE. However, there are substantial differences in clinical and histopathological features between the two types of skin lesion. Therefore, differentiation of SS from SCLE/SLE and significance of

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E-mail address: katayama@derma.med.osaka-u.ac.jp.

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diversified skin manifestations seen in SS patients are most important issues should be dissolved. Although significance of cutaneous manifestations in SS have been gradually recognized in rheumatologists as described above, sudomotor function has not been fully evaluated and recognized in the diagnosis of SS except for dermatologists.

Diagnosis of Sjögren syndrome

Diagnostic criteria has been proposed from several research groups in the different countries. In 1993, Vital proposed preliminary criteria for the classification of SS considering 4 different classifications (Copenhagen, Greece, Japan, and California).⁶ Since then, this classification had been preferentially used for the diagnosis of SS in the world and was revised in 2002.⁷ In 1999, Japanese research group also proposed revised Japanese criteria for SS.⁸ This criteria adopted positive anti-SSA/SSB antibodies and new diagnostic procedure to evaluate oral and ocular dryness following Vital's 1993 classification, except omission of sicca components. Common items in these criteria include subjective oral and ocular symptoms and objective laboratory test shown in Table 1: dry eye (item I) and dry mouth (item II), positive for keratoconjunctivitis sicca (KCS) (item III), a positive lip biopsy (item IV) and positive results for the assessment of salivary glands (item V), positive anti-Ro/La antibodies in the sera (item VI): Primary SS is usually classified as glandular type and extraglandular type and secondary SS is diagnosed when the patients fulfill the diagnostic criteria of other connective tissue diseases.

Pathomechanisms of Sjögren syndrome

Prevalence of SS among autoimmune diseases has been reported in the literatures. Oaane study demonstrates that more than 2 million SS patients are present in the United States.⁹

Table 1
Revised international classification criteria for Sjögren's syndrome.

I. Ocular symptoms: a positive response to at least one of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
II. Oral symptoms: a positive response to at least one of the following questions:
1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?
III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:
1. Schirmer's I test, performed without anaesthesia (5 mm in 5 min)
2. Rose Bengal score or other ocular dye score (4 according to van Bijsterveld's scoring system)
IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score 1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm ² of glandular tissue ¹⁸
V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:
1. Unstimulated whole salivary flow (1.5 ml in 15 min)
2. Parotid sialography showing the presence of diffuse sialectasias (punctuate, cavitary or destructive pattern), without evidence of obstruction in the major ducts ¹⁹
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer ²⁰
VI. Autoantibodies: presence in the serum of the following autoantibodies:
1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Adapted from the Ref. Vitali *et al.*⁷ with permission.

Pathomechanisms of SS have been also reported in the literatures. Figure 1 summarized the current understanding of mechanisms of induction of autoimmune sialoadenitis including sweat duct involvement. Most of the infiltrating cells are CD4(+), CD45RO(+), T cells.¹⁰ These cells express oligo clonal T cell receptor Vβ2/13, produce IL6 and TGFβ and destruct epithelial cells through FAS/FAS-L system. CD8(+) T cells, although minor populations, injure salivary gland by perforin/granzyme.¹¹ Tissue specific auto antibodies such as anti-arura Fording antibody or anti-muscarinic M3 receptor (M3R) antibody are also speculated to play some roles in induction of SS.¹² Latent viral infections such as EB, HTLV, HCV, HIV, HHV8 or cytomegalic virus are speculated to induce autoimmune response as well as other collagen diseases such as rheumatoid arthritis. Recent reports suggest microchimerism of chromosome Y might be the target of autoimmune response in a similar manner to GVHD. In the recent reports, significant number of Th17 cells are shown to infiltrate salivary gland, however their role of induction of sialoadenitis has not been fully understood.¹³

Cutaneous manifestations of Sjögren syndrome

We made a retrospective analysis from 1990 to 1996 on the cutaneous manifestations of the patients with SS who visited the outpatient clinic at Tokyo Medical and Dental University. Table 2 shows the prevalence of cutaneous manifestations observed in primary SS at the first consultation or during the clinical course.¹⁴ Most frequent skin manifestation is pernio-like erythema followed by angular cheilitis with red flat tongue, blepharitis, annular erythema, and drug eruptions. In addition to these cutaneous manifestations, we reported that hypohidrosis or impaired sweating functions sometimes trigger the asteatotic eczema, and cutaneous amyloidosis. Among these skin manifestations, we would like to focus on the clinical characteristics of hypohidrosis or anhidrosis and related skin dryness. These skin manifestations might be useful clues for the diagnosis of SS in dermatological fields.

Impaired sweating as an exocrine manifestation in Sjögren syndrome

Xerophthalmus or xerostomia are important symptoms affecting QOL of the patients with SS. CD4(+) or CD8(+) T cells infiltrating lacrimal or salivary glands are thought to destruct glandular cells resulting in sicca symptoms in SS.¹¹ In addition to these sicca symptoms described in the diagnosis criteria, hypohidrosis or anhidrosis associated with SS have been rarely reported in the literatures. These cutaneous manifestations related to sweat gland involvement in SS are not fully recognized in the field of rheumatologists and underestimated. To examine the prevalence of hypohidrosis and to evaluate sweating as an exocrinopathy in SS, 49 patients with SS (primary form, 38; secondary form were studied.¹⁵ Sweating was induced by mental stimulation such as deep breathing or hand grasping. Statistically significant reductions of sweat volume were seen in SS. In a control study, only hemodialysis patients showed impairment of sweating and this was greater than in patients with SS aged under 50 years. Patients under 50 years old showed impaired sweat function compared with normal controls. Urinary β2 microglobulin, salivary flow or lacrimal flow showed negative correlations with sweat volume (Unpublished observation). These results suggest that patients with SS develop impaired sweating as an exocrine manifestation in addition to the known symptoms of xerostomia and xerophthalmus. Recent studies demonstrated that water specific channel proteins play important roles in water trafficking in lacrimal or salivary gland in SS. These channel proteins are designated as aquaporin (AQP) and 13 aquaporin members are known at present. Among

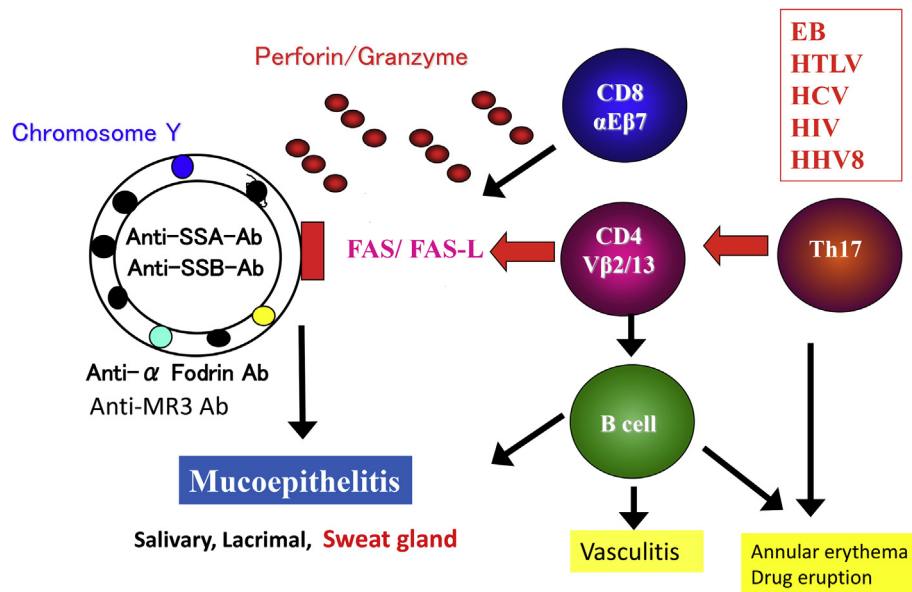


Fig. 1. Pathomechanisms of SS. Most of the infiltrating cells are CD4⁺ T cells. These cells destruct epithelial cells through FAS/FAS-L system. CD8⁺ T cells, although minor populations, injure salivary gland by perforin/granzyme. Tissues specific autoantibodies such as anti- α Fodrin antibody or anti M3 muscarinic receptor (MR3) antibody are also speculated to play some role in induction of SS. Latent viral infections such as EB, HTLV, HCV, HIV, HHV8 or cytomegalovirus are speculated to induce autoimmune response. Recent reports suggest michorichimerism of chromosome Y might be the target of autoimmune response in a similar manner to GVHD. Mucoepithelitis, cutaneous vasculitis, annular erythema or drug eruptions are frequently observed in SS.¹⁴

Table 2
Cutaneous manifestations in SS.

Cutaneous manifestations	Primary SS (N = 77)	Secondary SS (N = 25)	Total (N = 102)
(1)Related to glandular manifestations			
Cheilitis	17	9	26
Blepharitis	15	2	17
Xerotic eczema/Dry skin	7	6	13
Prurigo (?)	3	4	7
Ranula	3	0	3
(2)Related to B lymphocyte activation			
Pernio like erythema	19	7	26
Raynaud phenomenon	2	14	16
Livedo	3	3	6
Stasis dermatitis	4	1	5
Vasculitis/Skin Ulcer	2	3	5
Purpura	2	1	3
Mucionosis	2	0	2
Drug eruption	8	2	10
Cutaneous amyloidosis	4	2	6
Mosquito allergy	2	0	2
Lymphoma	1	1	2
Exsudative erythema (?)	5	4	9
Erythema nodosum	1	0	1
(3)Related to aberrant immune response			
Alopecia	7	4	11
Lichen planus	6	1	7
Psoriasis	4	1	5
Vitiligo	2	0	2
Sweet disease	1	0	1
Sarcoidosis	0	0	0
Contact dermatitis	4	1	5
(4)Infection			
Herpes infection	5	0	5
Erysipelas	2	0	2
Tuberculid	1	0	1
(5)Others			
Melamiosis (facial pigmentation)	4	4	8
Annular erythema	8	0	8
Tongue cancer	1	0	1

Modified from the Ref. Katayama¹⁴ with permission.

these AQP5, AQP5 labelling of salivary gland from SS patients is higher at the basement membrane, and lower at the apical membrane of acinar cells which contrasts to normal distribution pattern of the gland from normal subjects.¹⁶ This aberrant distribution pattern of AQP5 might be responsible for sicca symptoms seen in SS, however distribution of AQP5 in sweat gland has not been reported as yet.

In addition to the psychogenic sweating, we performed acetylcholine induced sweating function in SS.¹⁷ Similar results were obtained in a similar manner to decreased sweating functions measured by quantitative sudomotor axon reflex test (QSART) method. In SS, direct sweating as well as axon reflex mediated sweating were impaired, which suggests that autoimmune mechanisms might induce impaired sweating in SS which requires systemic steroid therapy.¹⁸

Table 3
Classification of anhidrosis.

Congenital	- Fabry disease - Congenital insensitivity to pain with anhidrosis - Congenital ectodermal dysplasia
Acquired	Secondary • Eccrine sweat gland/duct abnormality • Sympathetic nerve disturbance - Central: Horner syndrome, brain stem damage - Peripheral: polyneuritis • Autoimmune disease: Sjögren's syndrome, SLE • Diabetes mellitus • Drug induced (Atropine etc.) Associated with skin diseases - Miliaria - Atopic dermatitis (Inflammatory skin disease) - Ichthyosis - Psoriasis, Lichen planus (keratotic disorder) Idiopathic - Acquired idiopathic - generalized anhidrosis (AIGA)
	- Sudomotor neuropathy - IPSF idiopathic pure sudomotor failure - Sweat gland abnormality

Modified from the Ref. Ohshima and Tamada⁴⁰ with permission.



Fig. 2. Clinical features of Sjögren syndrome complicated with atopic dermatitis. (A) Patient 1: Lichenified and crusted lesions are present on the cubital fossa and wrist (B) Patient 2: Diffuse erythema and lichenified eczematous lesions are observed on the trunk skin. (C) Patient 3: Diffuse erythematous scaly patches with crusted and papular eruptions were observed on her face, scalp, and dorsal aspect of the hands. (D) Patient 4: Pruriginous crusted papules are present on the back. These 4 cases are from the reference Kitaba *et al.*³¹ and modified with permission. (E), (F) New added case 5 with prominent xerotic skin and pruriginous eruptions.

Sweating functions in SS complicated with atopic dermatitis

Although the prevalence of adult atopic dermatitis in Japan is 6.9%,⁸ complication of AD by SS is relatively rare and few case reports are available in the literature except in the setting of SLE.^{19,20} Table 3 is the proposed classification of anhidrosis. SS is classified into secondary anhidrosis secondary to peripheral sympathetic nerve disturbance. However, several reports suggested that hypohidrosis observed in SS is induced by autoimmune response including CD8⁺ T lymphocytes and anti-muscarinic M3 antibody in a similar manner to the destruction of salivary or lacrimal gland.¹⁸ Atopic dermatitis also has been also accompanied by dry skin and scratched eczematous lesions due to hypodermis possibly operated by histamine or substance P as reported by us.²¹ The involvement of Th17 cells in both SS¹³ and AD,²² as well as the Th1 and Th2 balance theory are thought to be responsible for the rare complication of these allergic and systemic autoimmune diseases. In SS, sweating induced by both the direct action of acetylcholine and the axon reflex is impaired, possibly due to eccrine gland dysfunction resulting from autoimmune mechanisms mediated by CD8⁺ T cells²³ or M3 receptor-specific autoantibodies²⁴ as previously described. It is well known that dry skin is occasionally seen in SS and clinical use of muscarinic M3 receptor agonists occasionally improves this condition through recovery of sweating function.²⁵ In regard to the sweating function in AD, it is well known that sweating may cause itching and secondary eczema; however, the results of previous studies on sweat-gland function in AD are controversial. Sweat secretion has been reported to be decreased,^{26,27} increased,^{28,29} or normal³⁰ in various experimental

studies of AD. Our previous observation on sweating function using QSART clearly demonstrated that reversible impairment of sweating function is present in AD. Most previous investigations assessed sweating function using a direct stimulation sweating test in which intradermal acetylcholine injection resulted in direct sweat responses.^{25–27} To clarify sweat function in AD and SS, we evaluated the postganglionic sweat output, which reflects axon reflex-

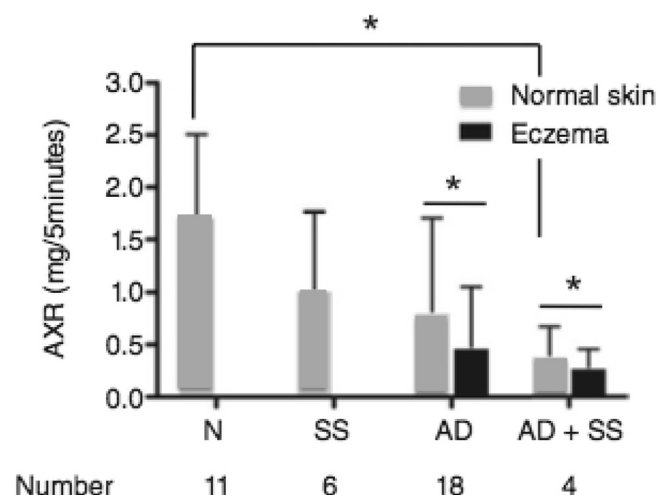


Fig. 3. Sweating functions in SS/AD overlap syndrome. Sweat volume of AXR in normal skin (normal control, SS, AD and AD/SS) and lesional eczematous skin (AD, and AD/SS). *p < 0.05. AXR, Axon reflex-mediated sweating.

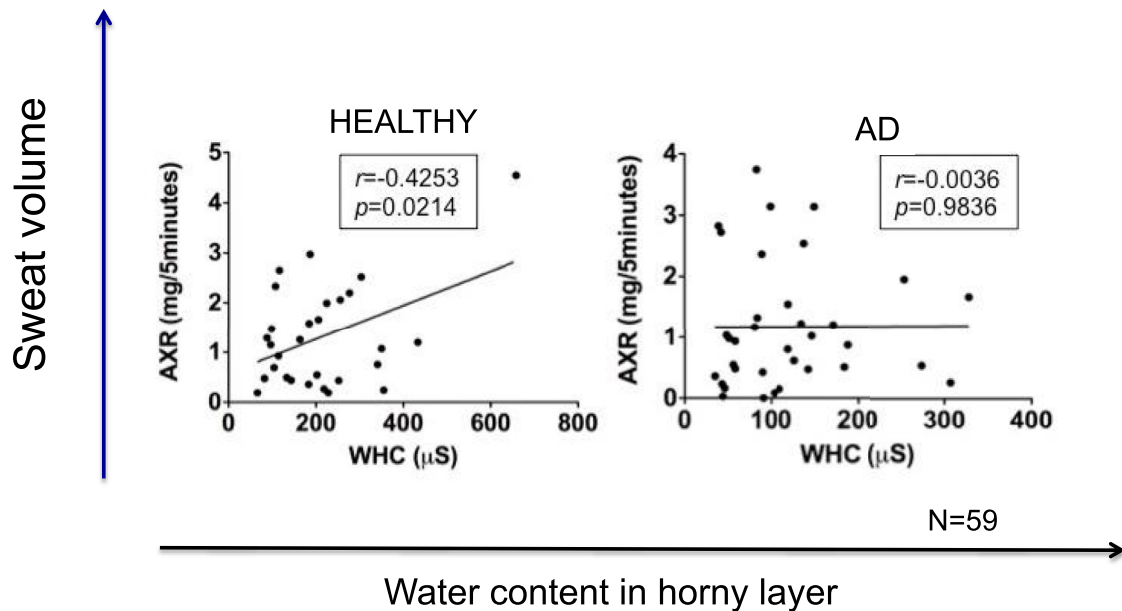


Fig. 4. Relationship between sweating and water content in the horny layer. Clear correlation ship between sweating function and water content in the horny layer is observed in normal control, but not in AD. This might be attributable to the degree of skin barrier function at the time of QSART analysis which control the dehydration of water from horny layer.

mediated sweating function of 4 cases with AD/SS, using QSART³¹ system (Fig. 2A–D). Another clinical features of AE/SS with prurigo was shown in Figure 2E, F with prominent xerotic skin (60 year female).

In the present cases, axon reflex induced sweating (AXR) sweat volumes were reduced and latency time prolonged in both non-lesional and lesional skin of AD/SS patients compared to those in non-atopic controls, and the reduction was greater in AD/SS (Fig. 3). In contrast to patients with AD, the DIR response characterized by exocrine gland dysfunction in patients with SS^{15,32,33} was significantly reduced compared to that in normal AD skin or healthy controls. The reason for normal directly stimulated sweating (DIR) in normal skin of AD/SS patient is unclear at present. The presence

of atopic skin lesions may modulate sweating function in normal skin of AD/SS by possible compensatory mechanisms. Recent reports have suggested that the barrier function, including trans epidermal water loss (TEWL) recovers or that ceramide content in the stratum corneum returns to normal levels when eczematous changes are resolved.^{34,35}

Figure 4 shows the relationship between sweating function and water content in the horny layer of normal and AD. Clear correlation ship between sweating function and water content in the horny layer is observed in normal control, but not in AD. This might be attributable to the degree of skin barrier function at the time of QSART analysis which control the dehydration of water from horny layer. Filaggrin deficiency might reduce sweat derived water

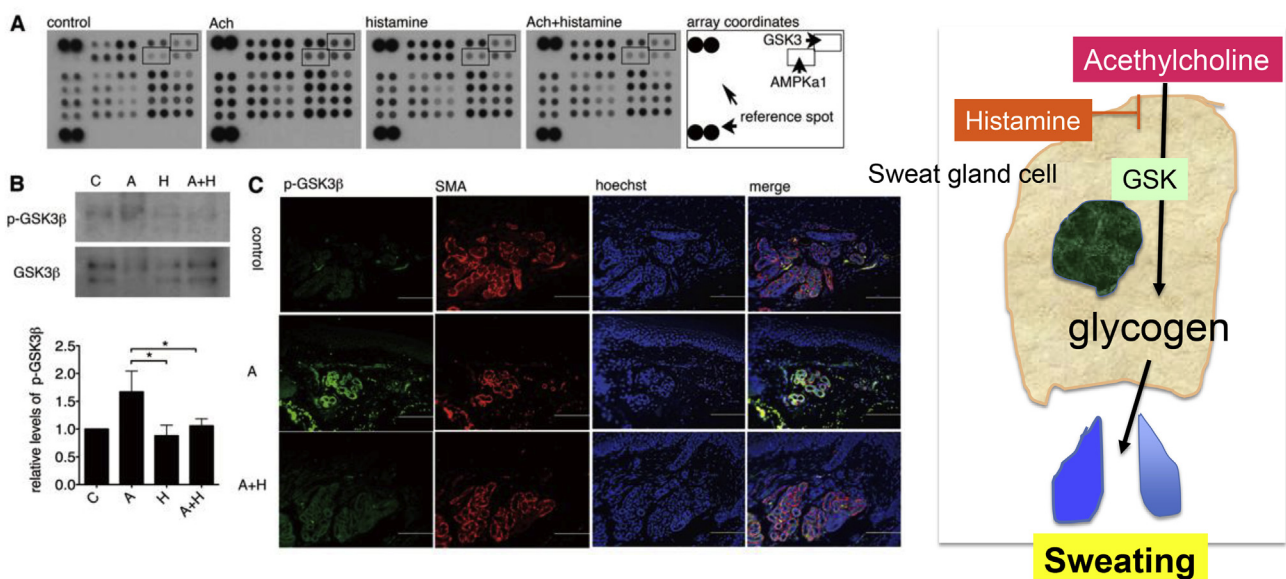


Fig. 5. Histamine downregulates acetylcholine induced-phosphorylation of glycogen synthase kinase. Acetylcholine (Ach), AMP activated kinase (AMPK), Smooth muscle actin (SMA). Kinase array: GSK3β is phosphorylated by acetylcholine but not by histamine. Modified from the reference Matsui *et al.*²¹ with permission.

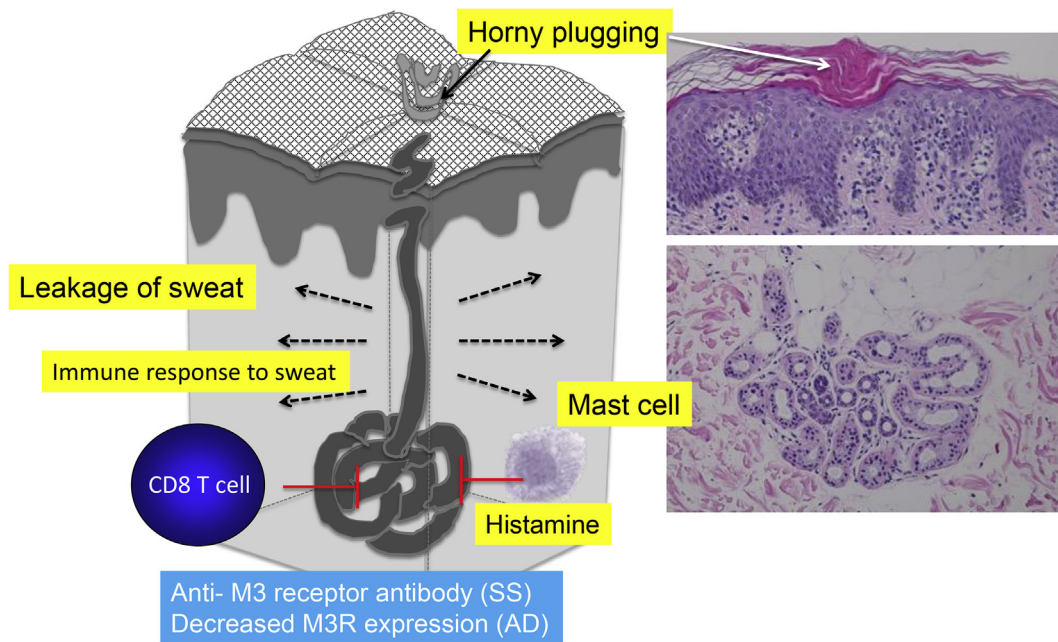


Fig. 6. Mechanisms of hypoidrosis in allergic skin diseases.

holding in the horn layer or high water content in the horny layer might decrease sweating. In addition, we recently reported that histamine downregulates acetylcholine induced-phosphorylation of glycogen synthase kinase resulting in impaired sweating which might suggest that severe allergic inflammation induces hypoidrosis and xerotic irritable skin in AD (Fig. 5, 6).²¹ As can be seen in Figure 7, adult AD occasionally present deckchair sign (zebra band like-features with normal skin fold and erythematous lesions of non-fold skin which might suggest the importance of horny layer humidity in AD.

Future perspective

Sweat secretion from eccrine glands is controlled by the sudomotor fibers of the sympathetic nervous system through postganglionic fiber stimulation of sweat glands by acetylcholine, which reflects autonomic nervous system function. Low *et al.* reported that when postganglionic sudomotor fibers are damaged, the AXR sweat response occurs earlier than the DIR response.³⁶ Therefore, evaluating the AXR response appears to be more reliable than evaluating the DIR response. Several reports concluded

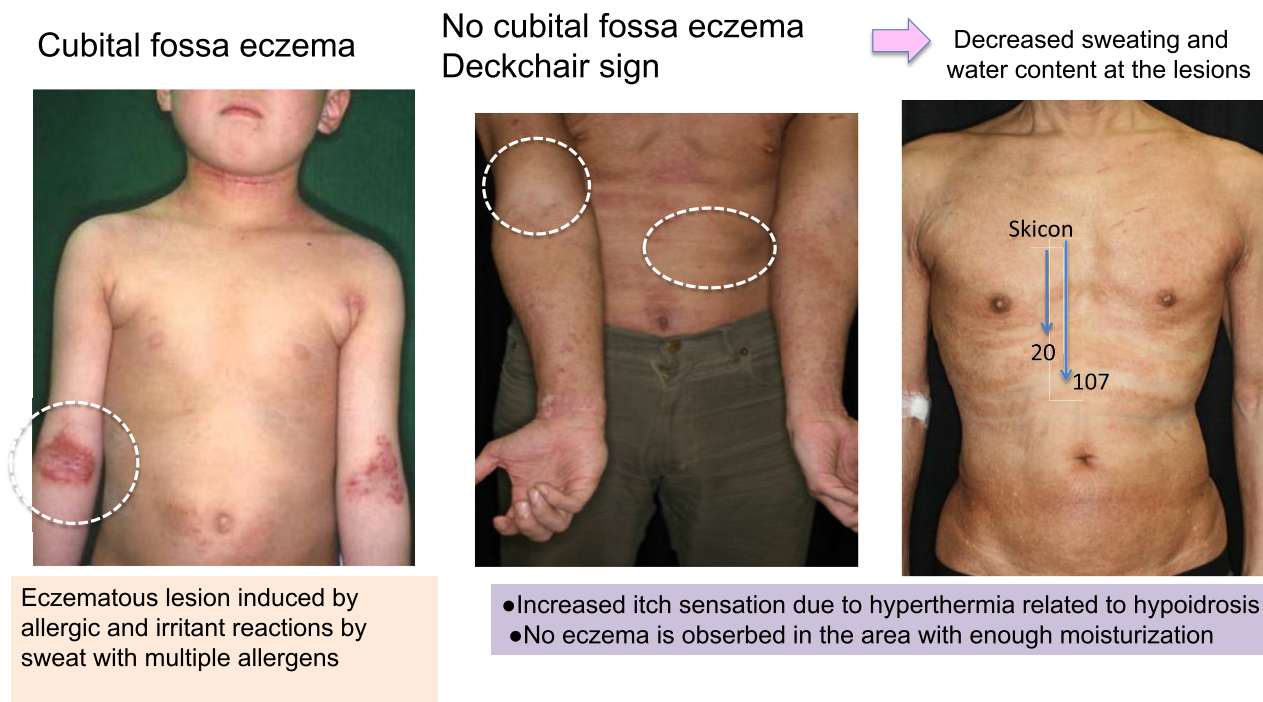


Fig. 7. Clinical features of AD with or without cubital fossa eczema. Adult AD occasionally present deckchair sign (zebra band like-features with normal skin fold and erythematous lesions of non-fold skin which might suggest the importance of horny layer humidity in AD. Skicon means water contents in the horny layer.

that the impaired sweating observed in AD is induced by damage to eccrine gland and/or ductal components secondary to dermal or epidermal inflammation.^{37,38} The results of nearly normal DIR responses in AD patients in the present study may contradict this inflammation theory because AD patients showed nearly normal sweating in response to direct acetylcholine stimulation, which excludes the occurrence of obstruction of the sweat ducts or hypo production of sweat by eccrine glands. In contrast to patients with AD, the DIR response in patients with SS, which is characterized by exocrine gland dysfunction^{15,32,33} was significantly reduced when compared with that in healthy controls. The lack of obstruction of the sweat ducts in serial sections of lesioned AD skin would also exclude the presence of organic changes in eccrine sweat ducts, although electron microscopic examination was not performed in this study. We conclude that the sweat glands are functionally intact in AD, while the autonomic nervous system is disturbed in lesioned and non-lesioned AD skin. Possible tolerance to cholinergic stimulation, manifesting as a higher sudomotor nerve excitation threshold or negative feedback, may be controlled in patients with severe AD by psychosomatic or unknown factors that could be therapeutic targets in adults with refractory disease. Further studies are needed to elucidate autonomic nervous system function in this regard. Finally, in a clinical practice, sweating is cited as the major exacerbating factor in adults with refractory AD. This contradictory result might be explained by the compensation theory of sweating. Shih *et al.* reported that individuals who experience hyperhidrosis of the palms and soles had a much smaller sweating response on the forehead, upper chest and arms.³⁹ It is possible that total sweating volumes from the skin surface in humans are equal, i.e. if sweating from one part of the skin decreases, then sweating elsewhere increases in compensation. We only measured sweating on the volar aspect of the forearm in this investigation. Therefore, increased sweating might have been observed if sweating were recorded on the flexor aspect of the elbow or neck, where eczematous lesions commonly appear in AD. This possibility should be clarified in the future for a better understanding of the pathogenesis and treatment of refractory AD and SS.

Conflict of interest

The author received honoraria from Maruho and Mitsubishi Tanabe Pharma.

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