

# Four Cases of Atopic Dermatitis Complicated by Sjögren's Syndrome: Link between Dry Skin and Autoimmune Anhidrosis

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## ABSTRACT

We report four adult cases of atopic dermatitis (AD) complicated by Sjögren's syndrome (SS). The patients fulfilled diagnostic criteria for AD and SS. All cases showed persistent itchy dry skin and eczematous lesions complicated by sicca symptoms including dry eyes and dry mouth with moderate joint pain. One case manifested annular erythema and another manifested widespread discoid erythema. To investigate the underlying cause of dry skin in these cases, sweating function was evaluated using a quantitative sudomotor axon reflex test (QSART) in which the axon reflex is stimulated by acetylcholine iontophoresis. The sweating latency time was significantly prolonged in eczematous skin of AD and AD/SS compared to normal controls. Axon reflex (AXR) sweat volume was also significantly reduced in AD (normal and eczematous skin) and AD/SS (normal and eczema) compared to normal control. In contrast, the direct sweat volume of lesional or non-lesional AD skin induced by direct stimulation with acetylcholine was only slightly reduced compared to that in normal controls, but not in SS and lesional skin of AD/SS patients. These results suggest that the impaired sweat response in AD is attributable to an abnormal sudomotor axon reflex, which is accelerated and modulated when complicated by SS resulting in dry skin in the present cases.

## KEY WORDS

atopic dermatitis, dry skin, hypohidrosis, QSART, Sjögren's syndrome

## INTRODUCTION

Dry skin, immunological dysfunction, increased IgE production, and an autonomic nervous system imbalance are frequently observed in patients with atopic dermatitis (AD), along with bronchial asthma or pollenosis, which have closely related genetic risk factors. Recent reports suggest that common loss-of-function variants of the epidermal barrier protein filaggrin are major genetic risk factors for AD.<sup>1-3</sup> Sjögren's syndrome (SS), another representative autoimmune disease with hypohidrosis, also manifests dry skin and might exacerbate dry skin in the setting of AD. Although the prevalence of AD and SS in the general population is not low, complication of

these diseases has been rarely documented. We report sweat function in four cases of AD associated with SS (AD/SS).

## CLINICAL SUMMARY

All patients fulfilled the diagnostic criteria for AD<sup>4</sup> and SS,<sup>5</sup> including moderate to severe, persistent itchy skin lesions and sicca symptoms of dry eyes and dry mouth with moderate joint pain. One case manifested annular erythema and another manifested widespread discoid erythema. Clinical profiles of the four patients are described in Table 1, 2, and clinical features are shown in Figure 1. The profile of Case 3 was described elsewhere.<sup>6</sup>

With the Institutional Review Board approval, a

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**Table 1** Clinical data related to atopic dermatitis

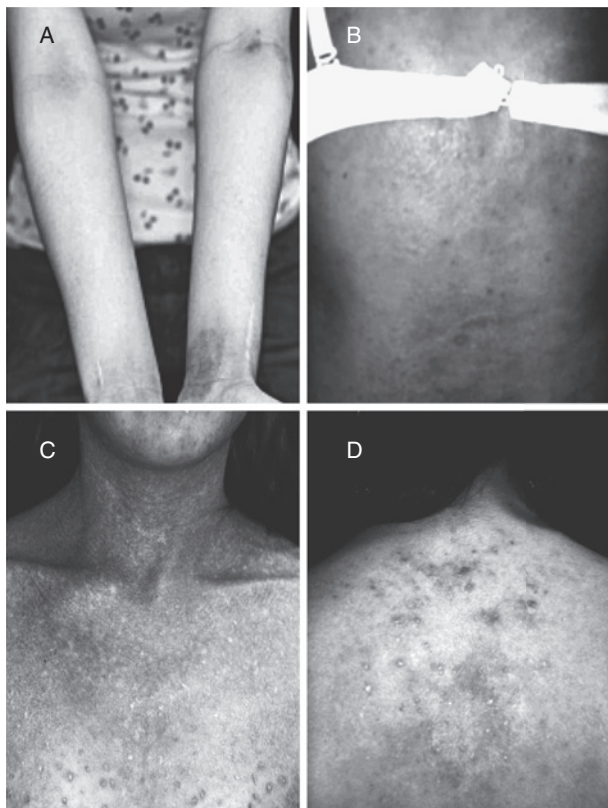
Case No.	Age	Gender	SCORAD	TARC (pg/ml)	IgE-RIST (IU/L)	Eosinophil (%)	Eosinophil (mm <sup>3</sup> )
1	29	female	35.2	497	298	3.7	192
2	32	female	49.5	1,596	6,790	14.1	1,112
3	32	female	60.3	2,363	15,300	6.3	306
4	17	male	25.3	224	124	7.3	392

SCORAD, severity scoring of atopic dermatitis; TARC, Thymus and activation regulated chemokine/CCL17 (pg/ml: normal < 400).

**Table 2** Clinical data related to Sjögren's syndrome

Case No.	Schirmer's test	Conjunctivitis	Lip biopsy (grade)	Gum test (ml/10 minutes)	Positive findings of salivary gland scintigram	Anti-SA ab (U/ml)	Anti-SB ab (U/ml)	IgG (mg/dl)	ANA	Anti DNA ab (IU/ml)
1	+	+	ND	5	-	-	62.1	1,633	-	-
2	+	+	ND	8	+	101	41.7	2,178	×80	-
3	+	+	3	8	+	68	-	4,478	×80	-
4	-	-	3	9	ND	122	183	1,727	×1280	-

ND, not done; ab, antibody.



**Fig. 1** Clinical appearance of the patients. (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, and (D) Patient 4: Pruriginous crusted papules are present on the back.

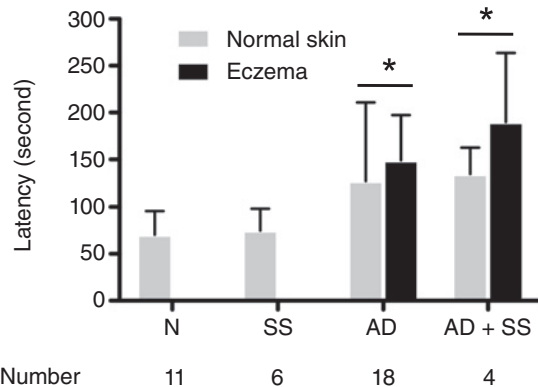
quantitative sudomotor axon reflex test (QSART) in which the axon reflex is stimulated by acetylcholine iontophoresis was performed as described previously.<sup>7</sup> Briefly, the subjects were asked to remain quiet in the measurement room before undergoing QSART. The two-channel type perspirometer (POS-02, Skinos, Co. Ltd., Nagoya, Japan) was used for the measurement of sweat volume. Acetylcholine induced-QSART (AXR sweating) was measured after iontophoretic application of acetylcholine (100 mg/ml) to the skin from the outer capsule using CI-5.0 (Skinos, Co.Ltd.). AXR sweat volume in the inner capsule separated by plastic wall from outer capsule was measured during 5 min of iontophoresis. Data for DIR sweating were obtained over the subsequent 5 min. Sweat onset time, i.e., the latency period from current loading to sweating (latency time), and sweat volume over 5 min were measured, and the area under the sweating curve was calculated during 0-5 min for AXR sweating and 6-11 min for DIR sweating (Table 3).

The latency time was significantly prolonged in AD (eczema) and AD/SS (eczema) compared to normal controls (N, Fig. 2) and AXR sweat volume was also significantly reduced in AD (normal and eczema) and AD/SS (normal and eczema) compared to normal controls (N, Fig. 3). In contrast, the DIR sweat volume of lesional or non-lesional AD skin was only slightly reduced compared to that in non-atopic controls, but that of lesional skin of AD/SS was apparently decreased without statistical significance (Fig. 4). These results suggest that the impaired sweat response in AD is attributable to an abnormal sudomotor axon reflex, which is accelerated and modulated when complicated by SS.

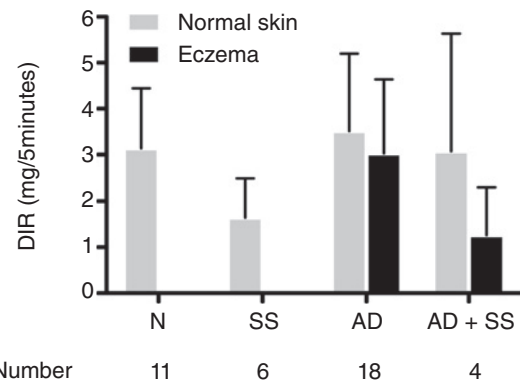
**Table 3** Measured values in quantitative sweat tests

Case No.	Latency (NL) seconds	Latency (L) seconds	AXR (NL) mg/5 minutes	AXR (L) mg/5 minutes	DIR (NL) mg/5 minutes	DIR (L) mg/5 minutes
1	107	143	0.145	0.354	1.224	0.735
2	143	155	0.314	0.367	1.775	2.801
3	170	161	0.353	0.388	2.455	0.975
4	120	300	0.785	0.040	6.839	0.543

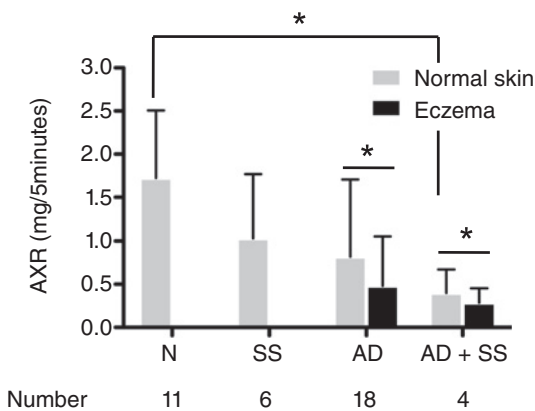
NL, non-lesional skin; L, lesional skin.



**Fig. 2** Quantitative sweating test. Quantitative sweating test was performed as previously described.<sup>7</sup> Latency period (seconds) in normal skin (normal control, SS, AD, and AD/SS) and lesional eczematous skin (AD and AD/SS). One-way ANOVA was used for the statistical analysis. \* $p < 0.05$ . AD (eczema) to normal control (N), AD/SS (eczema) to normal control (N), AD (eczema) to SS, and AD/SS (eczema) to SS. Number: case number.



**Fig. 4** Sweat volume of DIR in normal skin (normal control, SS, AD, and AD/SS) and lesional eczematous skin (AD and AD/SS). Number: case number.



**Fig. 3** Sweat volume of AXR in normal skin (normal control, SS, AD, and AD/SS) and lesional eczematous skin (AD and AD/SS). One-way ANOVA was used for the statistical analysis. \* $p < 0.05$  AD to normal control (N) and AD/SS to normal control (N). Number: case number.

**DISCUSSION**

Although the prevalence of adult atopic dermatitis in Japan is 6.9%,<sup>8</sup> complication of AD by SS is relatively rare and few case reports are available in the literature except in the setting of SLE.<sup>9,10</sup> The involvement of Th17 cells in both SS<sup>11</sup> and AD,<sup>12</sup> 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. Although it is conceivable that complication of two diseases is coincident, recent reports suggest ANA positivity in atopic dermatitis.<sup>13</sup> Therefore Sjögren's syndrome might exist in this populations of atopic dermatitis.

We previously reported that sweating function is impaired in patients with AD and primary SS compared to normal controls.<sup>7,14</sup> 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 cells<sup>15</sup> or M3 receptor-specific autoantibodies<sup>16</sup> as previously described. In contrast to SS, the reduced sweating function seen in AD is restricted only to axon reflex-induced indirect sweating, which is usually restored to normal levels after improvement of the dermatitis.<sup>7</sup> Therefore, xerotic skin lesions seen in the present cases might be due to additive AD- and SS-related hypohidrosis with accelerated dry skin. It is well known that dry skin is occa-

sionally seen in SS and clinical use of muscarinic M3 receptor agonists occasionally improves this condition through recovery of sweating function.<sup>17</sup>

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,<sup>18,19</sup> increased,<sup>20,21</sup> or normal<sup>22</sup> 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.<sup>17-19</sup> To clarify sweat function in AD, we evaluated the postganglionic sweat output, which reflects axon reflex-mediated sweating function, using QSART. In the present cases, 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. In contrast to patients with AD, the DIR response characterized by exocrine gland dysfunction in patients with SS,<sup>14,23,24</sup> was significantly reduced compared to that in normal AD skin or healthy controls. The reason for normal 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 TEWL, recovers or that ceramide content in the stratum corneum return to normal levels when eczematous changes resolve.<sup>25,26</sup> 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. Although complication of AD by SS disease has been rarely documented, it might be underestimated or overlooked in daily practice. For the skin care in AD, the complication of SS should be monitored, especially in adult AD patients.

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