

Periadnexal Mucin as an Additional Histopathologic Feature of Chronic Eczematous Dermatitis

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Background: Cutaneous mucinoses are a heterogeneous group of disorders characterized by an abnormal amount of mucin in the skin. However, the pathomechanism of an excessive mucin deposition in the skin is still unknown. Eczematous dermatitis is sub-classified histologically into acute, subacute, and chronic variants. The characteristic histopathologic findings for chronic eczema are variable. However, periadnexal mucin deposition is not known as a feature of chronic eczema. **Objective:** To evaluate the presence of periadnexal mucin deposition in chronic eczematous dermatitis. **Methods:** We analyzed the skin biopsy specimens from 36 patients who were pathologically diagnosed with chronic eczematous dermatitis. Alcian blue, colloidal iron, and periodic acid-Schiff stains were used to evaluate the mucin deposition in histologic sections. Two dermatologists and two dermatopathologists evaluated the degree of mucin deposition using a 4-point scale. **Results:** Various amounts of mucin deposition were observed in the periadnexal area of patients who were diagnosed with chronic eczema. Mucin deposition was more visible after staining with mucin-specific stains. Evaluation of the staining analysis scores revealed that the staining intensities were significantly higher in patients with chronic eczema than age- and site-matched controls (normal, acute to subacute eczema, and psoriasis vulgaris). **Conclusion:** Periadnexal mucin (secondary mucinoses) may be an additional finding of chronic eczematous

dermatitis. (*Ann Dermatol* 27(2) 133 ~ 141, 2015)

-Keywords-

Eczema, Periadnexal mucin, Mucinoses

INTRODUCTION

Cutaneous mucinoses are a heterogeneous group of disorders characterized by an abnormal amount of mucin in the skin¹. These mucinoses can be divided into two groups²: 1) primary cutaneous mucinosis, in which mucin deposition is the main histologic feature, resulting in clinically distinctive lesions; and 2) secondary mucinoses in which the deposition of mucin is an additional finding. The reason why excess mucin is produced in the skin is still unknown³. The clinical classification of eczema is not unified. However, it is generally classified as acute, subacute, or chronic eczema according to its etiology, skin manifestation, and the involved sites. However, the histopathologic classification of these three types is relatively precise. In particular, chronic eczema shows parakeratosis, hyperkeratosis, and acanthosis in the epidermis. In the dermis, there is fibrosis of the papillary dermis and numerous inflammatory cellular infiltrations. However, periadnexal mucin deposition is not known as an additional feature of chronic eczema.

We conducted this study to evaluate the periadnexal mucin deposition in chronic eczematous dermatitis.

MATERIALS AND METHODS

Case selection

We retrospectively reviewed patients' files from the Department of Dermatology, Yonsei University Wonju Severance Christian Hospital from January 2007 to December 2013. Patients with clinical features, including

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scales, lichenification, pruritus, and pathological features that were equivalent to chronic eczematous dermatitis (i.e., parakeratosis, hyperkeratosis, marked proliferation of the epidermis by acanthosis, fibrosis of the papillary dermis, and inflammatory cell infiltration of the dermis but not of the epidermis) were selected. Thirty-six patients (male [M] : female [F], 1.1 : 1) with a median age of 51.5 years were included in this study. The characteristics of

the patients are presented in Table 1. Age- and site-matched control samples were obtained from 30 patients who were diagnosed with acute eczema (M : F, 1 : 1; median age, 52 years) (Table 2) and from 20 patients with normal skin (M : F, 1 : 0.8; median age, 32 years). Twenty cases of psoriasis (M : F, 1 : 1; median age, 37 years) and other chronic inflammatory dermatoses were obtained to draw comparisons with the selected cases.

Table 1. Clinical data of patients with chronic eczematous dermatitis

No.	Age (y)	Sex	Clinical impression	Pathologic diagnosis	Biopsy site	Duration	Assessment of mucin staining
1	51	Male	Lichen simplex chronicus	Chronic eczematous dermatitis	Shin*	3 months	Weak
2	56	Male	Eczema	Chronic eczematous dermatitis	Dorsum of foot*	3 months	Moderate
3	2	Male	Insect bite	Chronic eczematous dermatitis	Thigh	3 months	Moderate
4	30	Male	Lichen simplex chronicus	Lichen simplex chronicus	Leg	3 months	Moderate
5	50	Male	Dermatofibroma	Prurigo nodularis	Inguinal area*	2 years	Weak
6	49	Female	Factitial dermatitis	Lichen simplex chronicus/ factitial dermatitis	Dorsum of hand*	6 months	Moderate
7	8	Female	Nummular eczema	Chronic eczematous dermatitis	Flank	2 years	Moderate
8	37	Male	Chronic eczema, Folliculitis, deep fungal infection	Chronic eczematous dermatitis	Calf	17 years	Moderate
9	60	Male	Photosensitive dermatoses	Chronic eczematous dermatitis	Hand*	2 months	Moderate
10	5	Male	Atopic dermatitis	Chronic eczematous dermatitis	Trunk	3 months	Strong
11	11	Female	Chronic eczema	Chronic eczematous dermatitis	Index finger*	5 years	Weak
12	22	Male	Chronic eczema	Chronic eczematous dermatitis	Neck	8 months	Weak
13	39	Male	Id reaction, syphilid, allergic contact dermatitis	Chronic eczematous dermatitis	Foot*	1 year	Weak
14	57	Female	Nummular eczema	Chronic eczematous dermatitis	Lower leg*	6 months	Moderate
15	76	Male	Chronic eczema	Chronic eczematous dermatitis	Neck	10 years	Moderate
16	22	Male	Nummular eczema	Nummular eczema	Forearm	3 months	Moderate
17	34	Female	Chronic eczema	Chronic eczematous dermatitis	Abdomen	3 years	Moderate
18	61	Male	Lichen simplex chronicus	Lichen simplex chronicus	Forearm	5 years	Moderate
19	81	Female	Chronic eczema	Chronic eczematous dermatitis with focal excoriation	Upper arm	3 months	Weak
20	75	Male	Lichen simplex chronicus	Lichen simplex chronicus	Dorsum of hand*	6 months	Moderate
21	57	Male	Chronic eczema	Chronic eczematous dermatitis	Lower leg	2 years	Moderate
22	62	Male	Eczema	Chronic eczematous dermatitis	Sole*	3 years	Weak
23	73	Female	Lichen simplex chronicus	Lichen simplex chronicus	Dorsum of foot*	10 years	Weak
24	66	Male	Chronic eczema	Chronic eczematous dermatitis	Inguinal area	2 years	Moderate
25	8	Female	Atopic dermatitis	Lichen simplex chronicus	Back	8 months	Strong
26	52	Female	Chronic eczema	Chronic eczematous dermatitis	Forearm	1 year	Moderate
27	34	Male	Lichen simplex chronicus	Lichen simplex chronicus	Shin*	3 years	Moderate
28	23	Female	Chronic eczema	Chronic eczematous dermatitis	Foot*	2 years	Weak
29	63	Female	Prurigo nodularis	Prurigo nodularis	Thigh	3 months	Moderate
30	58	Male	Nummular eczema	Chronic eczematous dermatitis	Foot*	9 months	Weak
31	72	Female	Chronic eczema	Chronic eczematous dermatitis	Dorsum of foot*	5 months	Moderate
32	12	Female	Atopic dermatitis	Chronic eczematous dermatitis	Shin*	3 years	Weak
33	66	Female	Chronic eczematous dermatitis	Chronic eczematous dermatitis	Upper arm	2 years	Moderate
34	39	Female	Lichen simplex chronicus	Lichen simplex chronicus	Lower leg	7 months	Moderate
35	56	Female	Chronic eczema	Chronic eczematous dermatitis	Dorsum of foot*	6 months	Weak
36	74	Female	Chronic eczema	Chronic eczematous dermatitis	Ankle*	2 years	Weak

*Cases which do not contain hair follicle in the slide sections.

Table 2. Clinical data of patients with acute eczema

No.	Age (y)	Sex	Clinical impression	Pathologic diagnosis	Biopsy site	Assessment of mucin staining
1	63	Male	Cellulitis, herpes simplex viral infection	Subacute eczematous dermatitis	Lower leg	Weak
2	70	Male	Xerotic eczema	Acute to subacute eczematous dermatitis	Leg	No staining
3	55	Female	Acute eczema	Acute eczematous dermatitis	Arm	No staining
4	37	Male	Autoimmune bullous dermatitis, irritant dermatitis	Acute eczematous dermatitis	Leg	No staining
5	19	Male	Tinea corporis, Darier's disease	Subacute eczematous dermatitis	Groin	No staining
6	42	Female	Chronic eczema, erythema nodosum	Acute eczematous dermatitis	Dorsum of hand	No staining
7	38	Female	Chronic eczema	Subacute eczematous dermatitis	Wrist	No staining
8	43	Male	Pityriasis rosea, erythema multiforme, allergic contact dermatitis	Subacute eczematous dermatitis	Lower leg	Moderate
9	16	Male	Atopic dermatitis	Subacute eczematous dermatitis	Thigh	Weak
10	59	Female	Wart, corn, knuckle pad	Subacute eczematous dermatitis	Index finger	No staining
11	14	Male	Tinea corporis, allergic contact dermatitis	Acute eczematous dermatitis	Neck	No staining
12	48	Female	Nummular eczema	Acute to subacute eczematous dermatitis	Lower leg	No staining
13	57	Male	Bowen's disease, allergic contact dermatitis	Subacute eczematous dermatitis	Posterior neck	Weak
14	26	Male	Subacute eczema, psoriasis	Subacute eczematous dermatitis	Forearm	Weak
15	36	Female	Erythema multiforme, erythema annulare centrifugum, erythema chronicum migrans, allergic contact dermatitis	Superficial perivenular lymphocytic infiltration with occasional eosinophils, suggestive of eczematous dermatitis	Flank	No staining
16	63	Female	Psoriasis	Subacute eczematous dermatitis	Arm	Weak
17	79	Female	Lichen amyloidosis	Subacute eczematous dermatitis	Arm	No staining
18	66	Male	Neutrophilic dermatosis, erythema elevatum diutinum, pompholyx, granuloma annulare	Acute eczematous dermatitis	Dorsum of hand	No staining
19	66	Male	Nummular eczema, guttate psoriasis	Subacute eczematous dermatitis	Lower leg	Weak
20	38	Male	Psoriasis, chronic eczema	Subacute eczematous dermatitis	Sole	No staining
21	77	Female	Xerotic eczema, Lichen simplex et chronicus, psoriasis	Acute to subacute eczematous dermatitis	Leg	No staining
22	19	Male	Tattoo granuloma, infectious granuloma	Acute eczematous dermatitis	Forearm	No staining
23	16	Female	Fixed drug eruption	Acute eczematous dermatitis	Forearm	Weak
24	64	Male	Allergic contact dermatitis, drug eruption	Acute eczematous dermatitis	Thigh	Weak
25	51	Female	Dermatitis herpetiformis, impetigo, allergic contact dermatitis	Acute eczematous dermatitis	Arm	Weak
26	20	Female	Eczema	Acute eczematous dermatitis	Leg	Weak
27	53	Female	Allergic contact dermatitis	Acute eczematous dermatitis	Arm	No staining
28	62	Male	Allergic contact dermatitis	Acute eczematous dermatitis	Abdomen	No staining
29	58	Female	Allergic contact dermatitis	Acute eczematous dermatitis	Leg	No staining
30	61	Female	Allergic contact dermatitis	Acute eczematous dermatitis	Neck	No staining

Tissue and histopathology

In this study, biopsied specimens were collected for routine diagnostic procedures. Skin samples were obtained under local anesthesia with 2% lidocaine using a 3-mm punch biopsy or incision. Eczematous dermatitis is histopathologically sub-classified into acute, subacute, or chronic variants. In chronic eczema, there are variable de-

grees of hyperkeratosis with hypergranulosis and psoriasiform hyperplasia; additionally, there are patchy infiltrations of chronic inflammatory cells and a fibrosed papillary dermis⁴.

Histology

The tissues were fixed in 10% phosphate-buffered formaldehyde and were embedded in paraffin. According to

standard procedures, the sections were stained with hematoxylin-eosin. Alcian blue, colloidal iron, and periodic acid-Schiff (PAS) were used as stains to evaluate the mucin deposition in the histologic sections.

Staining analysis

The mucin staining intensity was scored qualitatively on a 4-point scale: 0, no staining; 1, weak staining; 2, moderate staining; and 3, strong staining. The staining was evaluated by two dermatologists and two dermatopathologists.

Statistical analysis

PASW Statistics version 18.0 (IBM Co., Armonk, NY, USA) was used to perform all statistical analyses. We performed unpaired t-tests to compare the staining intensities among the chronic eczema, acute eczema, normal, and psoriasis groups. p -values < 0.05 were considered statistically significant.

RESULTS

Histology

The histopathological examination of the specimens revealed variable degrees of mucin deposition in the periadnexal area in patients diagnosed with chronic eczema. Mucin deposition was more visible after staining with mucin-specific stains. While the samples were stained positive

with Alcian blue (pH 2.5) and colloidal iron, they were stained negative with PAS. Mucin deposition in the periadnexal area was significantly higher in patients with chronic eczema than in the age- and site-matched controls (Fig. 1~4). Among psoriasis patients, none of the samples were stained with PAS, colloidal iron, or Alcian blue (Fig. 5). Only three samples were stained weakly when Alcian blue and colloidal iron were used as the staining agent. Among 36 slides, 18 in which hair follicles existed in the tissue specimens were stained weakly to strongly with colloidal iron (Fig. 6).

Staining analysis

The staining intensity scores were significantly higher in patients with chronic eczema than in those with acute eczema, psoriasis, or normal skin (all, $p < 0.01$) (Fig. 7).

DISCUSSION

Cutaneous mucinoses are a heterogeneous group of diseases characterized by the abnormal deposition of mucin, an amorphous substance composed primarily of hyaluronic acid and sulfated glycosaminoglycans⁵. Although many dermatologic diseases show cutaneous mucinoses and have considerable overlap in their characteristics, the underlying cause of abnormal mucin deposition is still in dispute⁶.

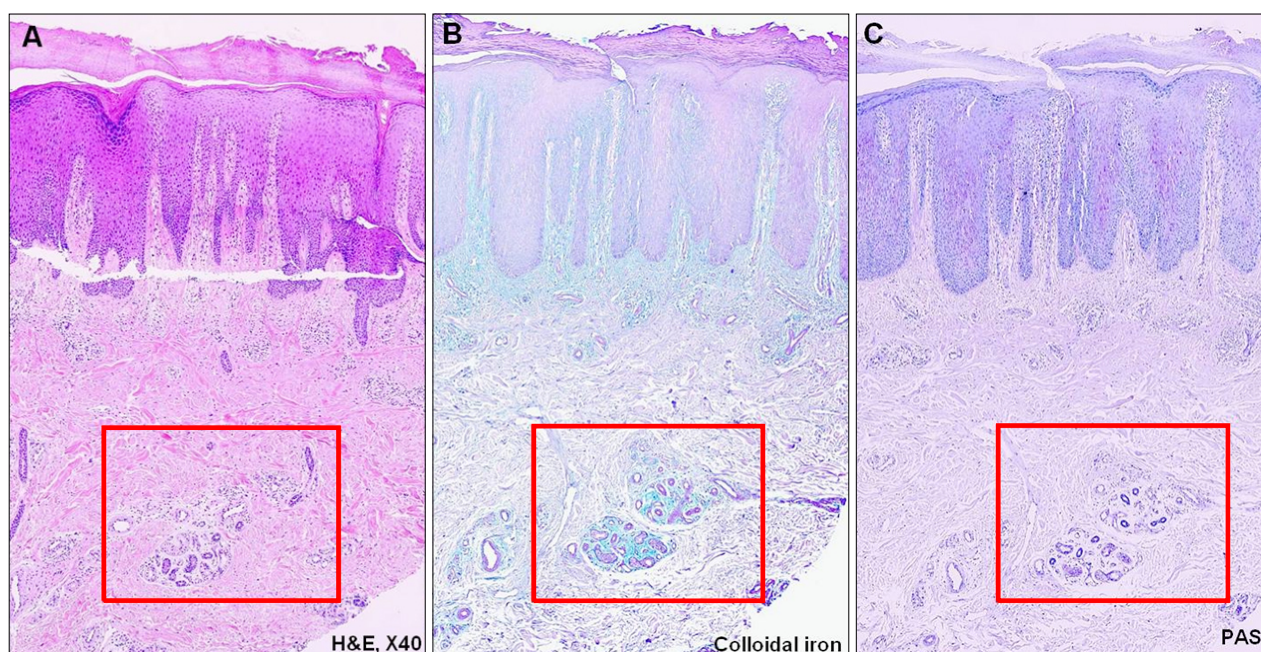


Fig. 1. Pathology of a 56-year-old male who is diagnosed with chronic eczema. (A) Periadnexal mucin deposition (H&E, $\times 40$), (B) mucin deposition is more visible when the slide is stained with colloidal iron ($\times 40$), and (C) the periodic acid-Schiff (PAS) staining is negative. These findings indicate that the mucin around the periadnexal area is dermal mucin, not epithelial mucin (PAS, $\times 40$).

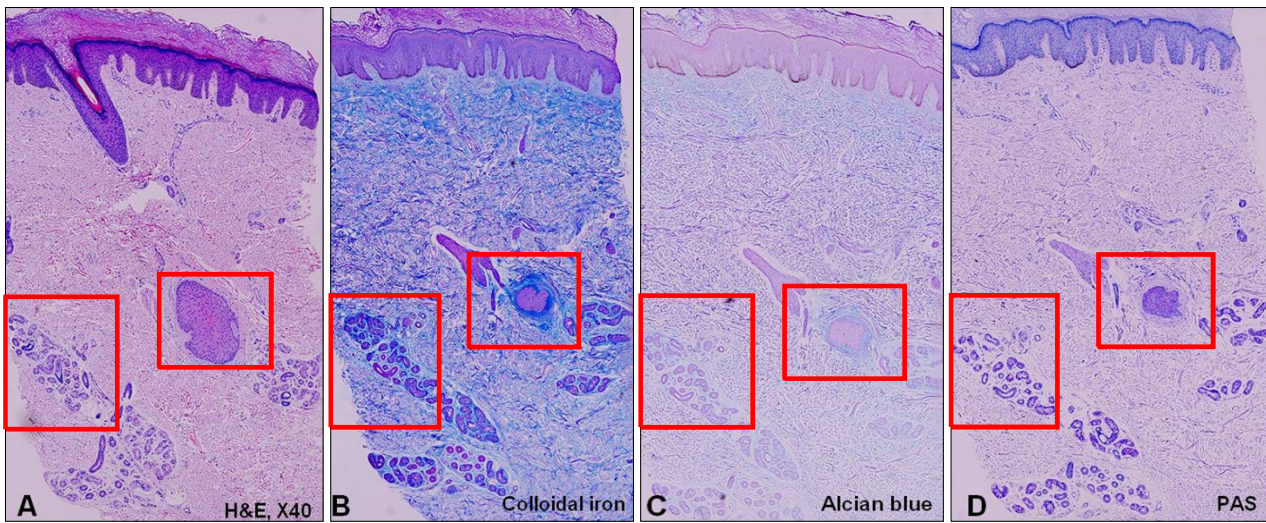


Fig. 2. Pathology of a 61-year-old male who is diagnosed with lichen simplex chronicus. (A) Chronic eczema showing periadnexal mucin deposition (H&E, $\times 40$), (B) the mucin deposition is clearly visible after staining with colloidal iron and (C) Alcian blue ($\times 40$), and (D) the periodic acid-Schiff (PAS) staining is negative ($\times 40$).

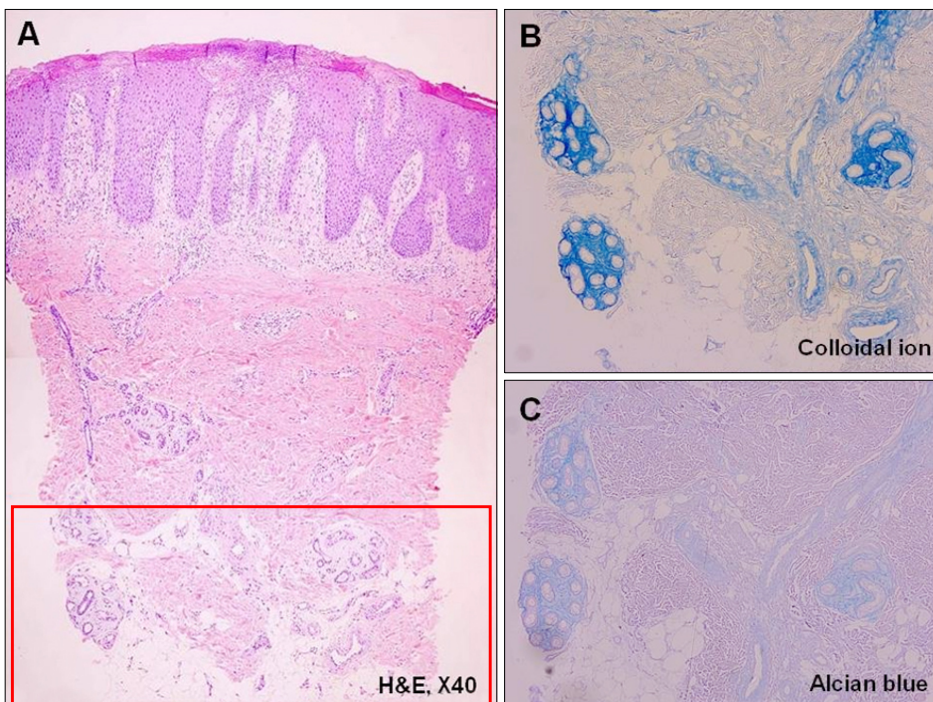


Fig. 3. Pathology of a 5-year-old male who is diagnosed with atopic dermatitis. (A) Chronic eczema showing periadnexal mucin deposition (H&E, $\times 40$), (B) the mucin deposition is more prominent after staining with colloidal ion, and (C) Alcian blue ($\times 200$).

Mucin, which is normally present in several organs, is sub-classified as epithelial and dermal mucin according to its composition. Epithelial and dermal mucins have different staining patterns. In the skin, epithelial mucin or sialomucin is present in the dark cells of the eccrine glands and in the apocrine secretory cells. Epithelial mucin contains neutral and acid glycosaminoglycans and stains with Alcian blue (pH 2.5) similar to dermal mucin, but it is PAS-positive and resistant to hyaluronidase². Conversely,

dermal mucin, which is normally produced by dermal fibroblasts, is present in the ground substance of the dermis. Dermal mucin consists of acid glycosaminoglycans, which are repeating polysaccharides that form complex carbohydrates. It stains with Alcian blue at a pH of 2.5 but not at a pH of 0.4; in addition, it is PAS-negative, stains metachromatically purple with toluidine blue at a pH of 4.0 but not at a pH of 1.5, and is sensitive to hyaluronidase². In this study, there were variable degrees of mucin deposi-

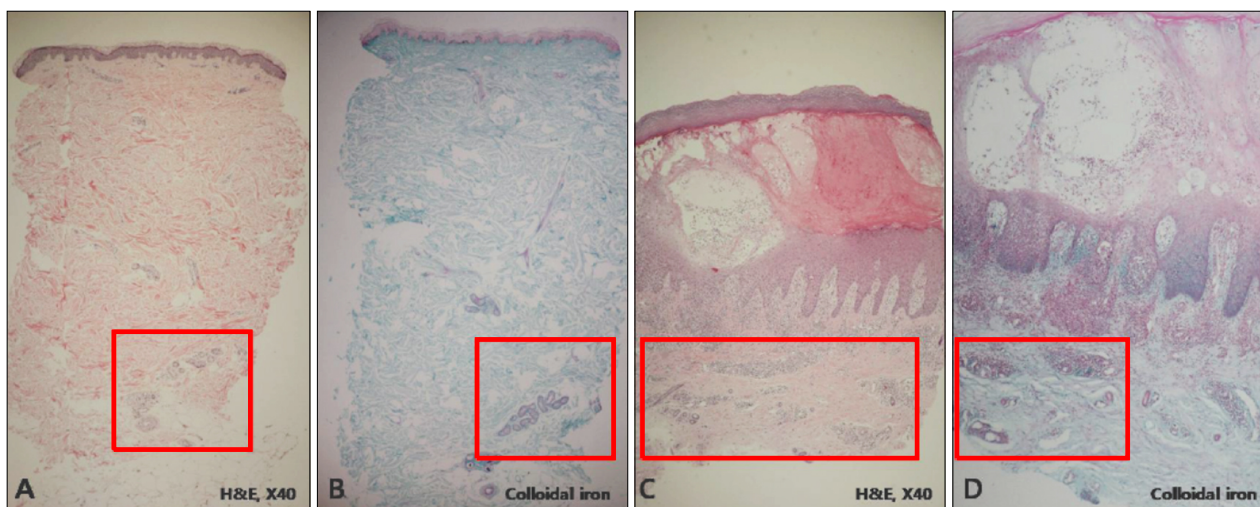


Fig. 4. Pathology of the control samples that are diagnosed with normal skin or acute eczema. Mucin deposition is less visible in the control samples. (A) Normal skin (H&E, $\times 40$), (B) normal skin (colloidal iron, $\times 40$), (C) acute eczema (H&E, $\times 40$), and (D) acute eczema (colloidal iron, $\times 40$).

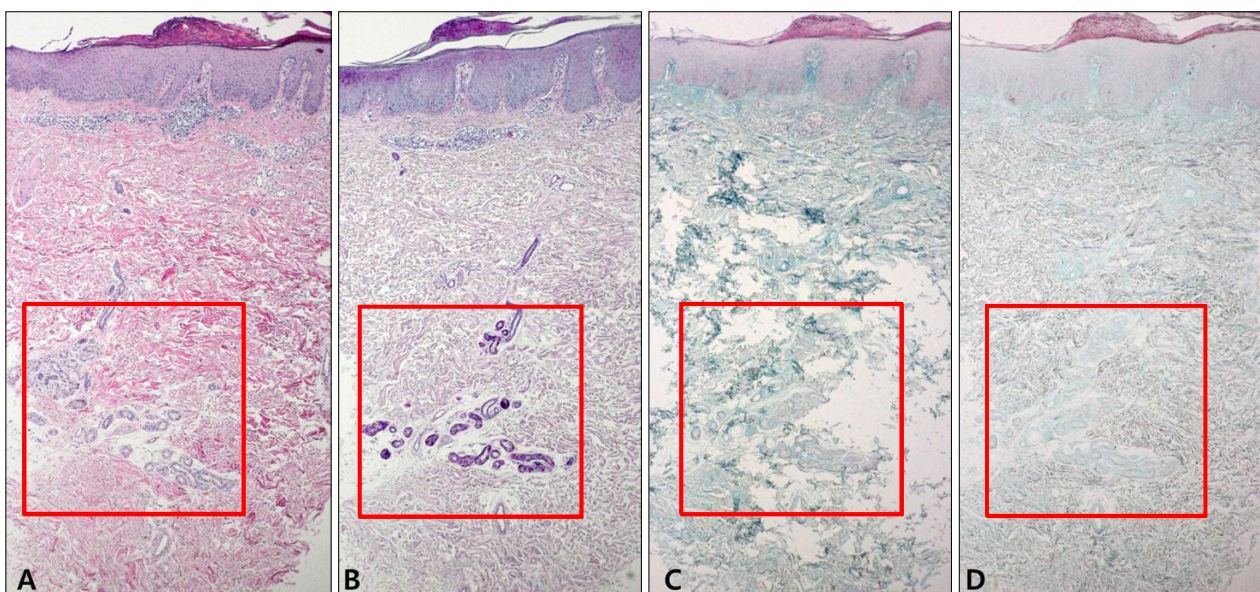


Fig. 5. Pathology of the control samples that are diagnosed with psoriasis vulgaris. (A) H&E ($\times 40$), (B) periodic acid-Schiff ($\times 40$), (C) Alcian blue ($\times 40$), and (D) colloidal iron ($\times 40$) staining are negative.

tion in the periadnexal area, especially in the perieccrine structure, in patients diagnosed with chronic eczema. Although they did not stain when PAS was used as a staining agent, the samples stained positively with Alcian blue (pH 2.5) and colloidal iron. These findings indicate that the periadnexal mucin present in the chronic eczematous patients was dermal mucin.

As previously mentioned, cutaneous mucinoses can be divided into primary cutaneous mucinoses and secondary mucinoses. Primary mucinosis consists of diffuse form and focal form. The former includes pretibial myxedema, gen-

eralized myxedema, scleredema, and reticular erythematous mucinosis. There are cutaneous focal mucinosis, myxoid cysts, follicular mucinosis, and acral persistent papular mucinosis in the latter. We believe that our cases were secondary dermal mucinoses, because the mucin deposition was not a main histologic feature of the chronic eczema.

The reason why mucin is abnormally produced in chronic eczema is unclear. Some studies have proposed possible pathomechanisms for the abnormal mucin production. Pandya et al.³ reported that certain types of serum factors

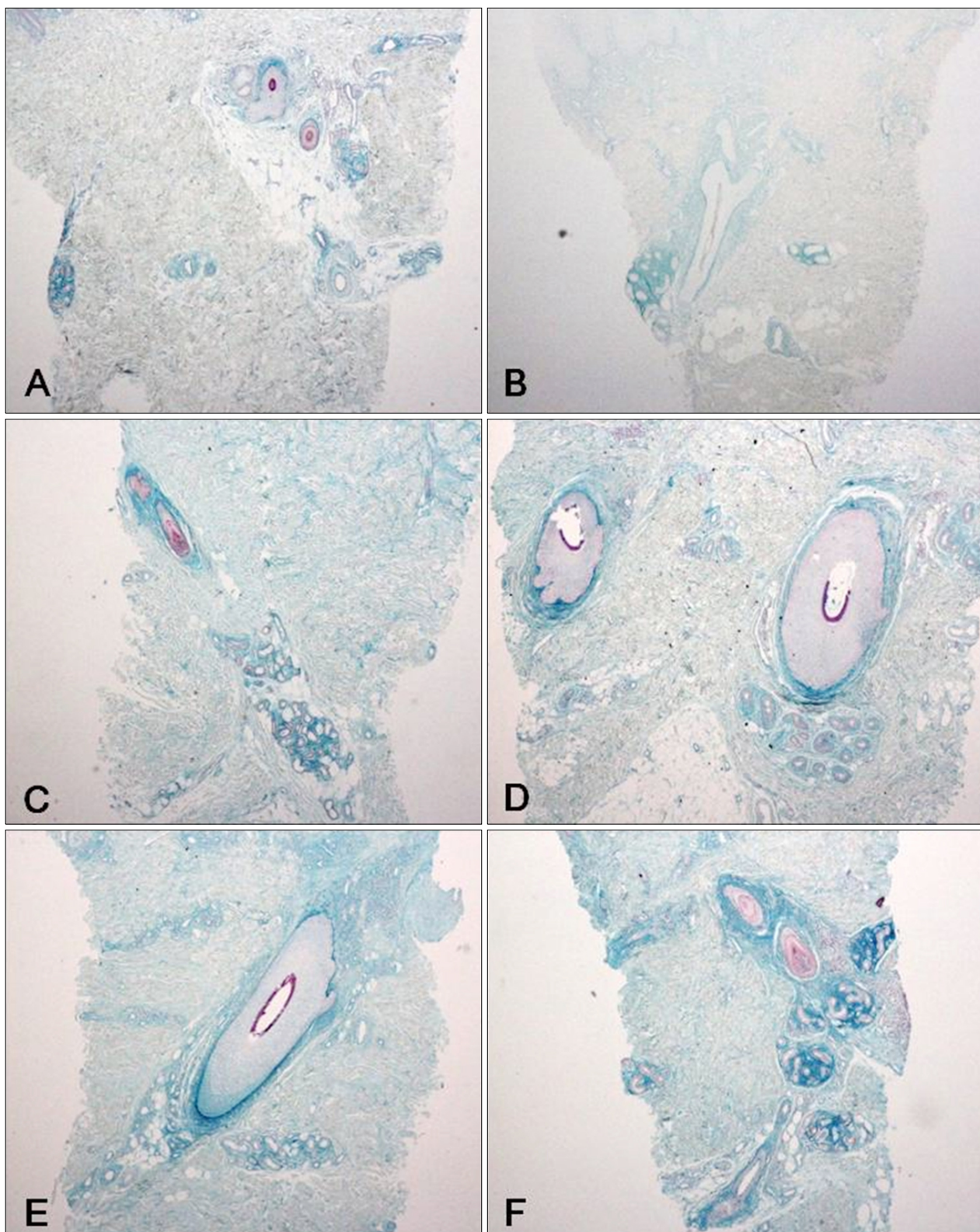


Fig. 6. Pathology of the patients diagnosed with chronic eczema with their hair follicles in the specimen (colloidal iron, $\times 100$). A, B: weak, C, D: moderate, E, F: strong.

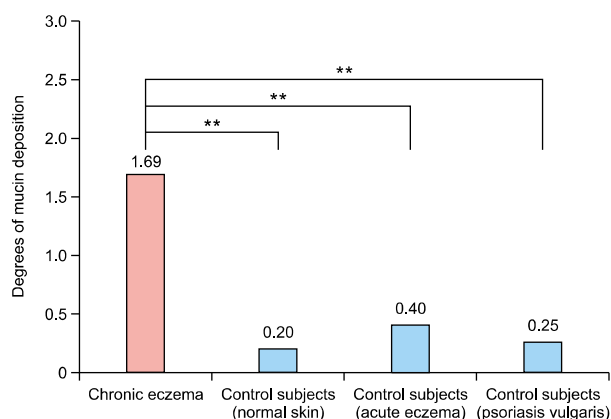


Fig. 7. Physician assessment of the mucin deposition using a 4-point scale. The staining intensities are significantly higher in patients with chronic eczema compared to those with acute eczema, psoriasis, or normal skin (** $p < 0.01$).

such as immunoglobulins or cytokines can stimulate glycosaminoglycan synthesis. Serum immunoglobulin levels or circulating autoantibodies are elevated in various dermatologic diseases such as lichen myxedematosus, Graves' disease-associated pretibial myxedema, and papulonodular mucinosis associated with lupus erythematosus^{7,8}. In addition, some cytokines are known to stimulate glycosaminoglycan synthesis in the skin. Interleukin (IL)-1, the tumor necrosis factors (TNF), and transforming growth factor are examples of these kinds of cytokines that can play a major role in glycosaminoglycan synthesis^{9,10}. There are some differences in cytokine expression according to the course of the disease. For example, expression of the cytokines IL-10, IL-6, interferon (IFN)- γ , IL-4, and TNF- α is significantly higher in the chronic state of atopic dermatitis than in the acute state¹¹⁻¹³. Although there are many mechanisms involved in the pathogenesis of psoriasis, from an immunologic point, the proliferation of keratinocytes is stimulated by diverse cytokines produced by T cells (IFN- γ , IL-2, and TNF- α) and keratinocytes (IL-6, IL-8, TGF- α , and β). IL-6, TNF- α , and IFN- γ are overlapping cytokines in eczema and psoriasis. However, there are some differences in the pathogenesis between the two diseases; that is, there are other factors that contribute to the pathomechanism. Therefore, we hypothesize that inflammatory cytokines associated with chronic eczema may stimulate glycosaminoglycan synthesis in the skin. Physician-assessed staining intensities of the mucin deposition were much higher in patients with chronic eczema than in a control group with acute eczema, psoriasis, and normal skin, and the differences were statistically significant. Mucin deposition in chronic eczema is mainly located in the periadnexal area, not the entire dermis. In addition, some degree of mucin deposition was also observed in

the papillary dermis. There was hardly any mucin deposition around the hair follicles in the tissues of the normal or acute eczema group, which included hair follicles on the slide. Of 36 specimens from the chronic eczema group, 18 slides in which hair follicle existed showed a weak to strong mucin deposition in the perifollicular area. The periadnexal area or adventitial dermis has different properties compared to the other reticular dermis and represents the effects of the epidermis¹⁴.

To clarify the histologic significance, we compared samples of chronic eczema with samples of psoriasis to other chronic inflammatory dermatoses. Compared to chronic eczema, none of the psoriatic samples stained well with colloidal iron or Alcian blue, while only three of 20 samples stained weakly with Alcian blue and colloidal iron. The intensity of mucin staining for psoriasis was lower than for acute and chronic eczema. Based on these findings, we think that periadnexal mucin deposition can be one of the differential points between chronic eczematous dermatitis and chronic papulosquamous dermatoses such as psoriasis.

In summary, we used a histological approach to demonstrate the presence of periadnexal mucin deposition in chronic eczematous dermatitis biopsy samples. These findings were consistent with secondary mucinosis, because the mucin deposition was not a pathognomic sign of chronic eczematous dermatitis. In addition, these findings were more prominent in chronic eczematous dermatitis than in normal skin, acute eczematous dermatitis, and psoriasis. Therefore, we propose that periadnexal mucin may be an unusual and additional histological finding of chronic eczematous dermatitis.

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