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
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 | Facitital dermititis | Lichen simplex chronicus/ factitial dermititis | 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 dermititis | 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 | Upper arm with focal excoriation | 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 | Shin* | 3 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 | Foot* | 2 years | Weak |
| 28  | 23      | Female | Chronic eczema    | Chronic eczematous dermatitis | Thigh | 3 months | Moderate |
| 29  | 63      | Female | Prurigo nodularis | Prurigo nodularis       | Foot* | 9 months | Weak |
| 30  | 58      | Male | Nummular eczema     | Chronic eczematous dermatitis | Foot* | 5 months | Moderate |
| 31  | 72      | Female | Chronic eczema    | Chronic eczematous dermatitis | Shin* | 3 years | Weak |
| 32  | 12      | Female | Atopic dermatitis | Chronic eczematous dermatitis | Upper arm | 2 years | Moderate |
| 33  | 66      | Female | Chronic eczematous dermatitis | Chronic eczematous dermatitis | Dorsum of foot* | 6 months | Weak |
| 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      | Male  | 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 degrees of hyperkeratosis with hypergranulosis and psoriasiform hyperplasia; additionally, there are patchy infiltrations of chronic inflammatory cells and a fibrosed papillary dermis.4

**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 periannexal 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 periannexal 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 glycosaminoglycans. Although many dermatologic diseases show cutaneous mucinoses and have considerable overlap in their characteristics, the underlying cause of abnormal mucin deposition is still in dispute.\(^6\)
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, ×40), (B) the mucin deposition is clearly visible after staining with colloidal iron and (C) Alcian blue (×40), and (D) the periodic acid-Schiff (PAS) staining is negative (×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, ×40), (B) the mucin deposition is more prominent after staining with colloidal iron, and (C) Alcian blue (×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, ×40), (B) normal skin (colloidal iron, ×40), (C) acute eczema (H&E, ×40), and (D) acute eczema (colloidal iron, ×40).

Fig. 5. Pathology of the control samples that are diagnosed with psoriasis vulgaris. (A) H&E (×40), (B) periodic acid-Schiff (×40), (C) Alcian blue (×40), and (D) colloidal iron (×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, generalized 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.\(^1\) 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, ×100). A, B: weak, C, D: moderate, E, F: strong.
such as immunoglobulins or cytokines can stimulate glycosaminoglycan synthesis. Serum immunoglobulin levels or circulating autoantibodies are elevated in various dermatologic diseases such as lichen myxedematous, Graves’ disease-associated pretibial myxedema, and papulonodular mucinosis associated with lupus erythematosus7,8. 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 synthesis9,10. 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 state11,12. 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, TFG-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, or normal skin (**p < 0.01). 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 mucinoses, because the mucin deposition was not a pathognomonic 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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