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【VI】

研究成果の刊行物・別刷り

Eosinophilic Pustular Folliculitis

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Introduction

Eosinophilic pustular folliculitis (EPF) is a noninfectious inflammatory skin disease characterized by eosinophilic infiltration mainly of hair follicles. This clinical entity is very memorable for Asian dermatologists because it was first described by Prof. Shigeo Ofuji of Kyoto University, Japan (Fig. 1). Although classic EPF has been reported mainly from Japan as well as other Asian countries, global dermatology has paid a considerable attention to EPF because immunosuppression-associated EPF was recognized as an HIV-related skin disease. In this Chapter, EPF will be reviewed from the standpoint of its etiology and pathophysiology, emphasizing the great contribution of Asian dermatologists to this Asia-originated, globally-acknowledged skin disease.

Definition and epidemiology

EPF was first reported in 1965 as a follicular variant of subcorneal pustular dermatosis[1], which was later named EPF in 1970 as a novel clinical entity by Ofuji[2]. This is why EPF is called Ofuji's disease, however, it should be noted that papuloerythroderma is sometimes referred as another Ofuji's disease[3] since it was also first described by Ofuji in 1984[4].

EPF manifests as chronic and recurrent itchy follicular papules and sterile pustules which enlarges peripherally with central clearing tendency. Histopathologically, it is characterized by the eosinophilic infiltrates in pilosebaceous unit.

EPF is now classified into 3 variants: Classic EPF, immunosuppression-associated EPF and infancy-associated EPF[5]. Classic EPF has been reported mainly from Asian countries. Epidemiological studies revealed that classic

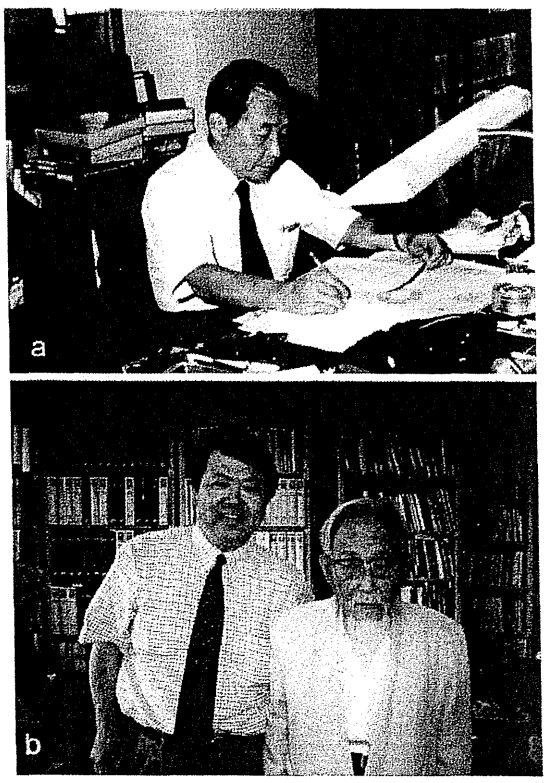

Fig. 1. Professor Ofuji, Kyoto University, Japan. (a) Before retirement in 1979. (b) Recent photograph in 2008 (Right), Left: Author (YM).

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EPF occurs in young adults of 20-30 years old and the male/female ratio is 4.8:1 in Japanese literature[6]. The most commonly affected lesion of classic EPF is the face (85%), however, the eruptions can be seen on the back, arms and the chest. Of great interest is that the eruption can be found on palms and soles in 22% of the patients[7]. One may infer that the term "folliculitis" seems to be inappropriate since 6% of the patients start only with palmoplantar pustular lesions, though 66% of them first appear on the face[8]. Although some papers proposed to use the term of sterile eosinophilic pustulosis[9] or eosinophilic pustular dermatosis[10], Prof. Ofuji insisted that the name of the disease should represent the characteristic features of the typical eruption, and thus the name of EPF should be kept irrespective of the palmoplantar lesions (personal communication). In his own review article, Prof. Ofuji mentioned that he personally had an impression that the classic EPF seemed to be more commonly observed in patients with a past history of acne[11].

Pathophysiology

At present, nobody can answer the questions why eosinophils are attracted in hair follicles, why peripheral number of eosinophils is increased, why the skin lesions flare up periodically, why pustules are observed in palmoplantar area or why EPF is frequently found in patients with HIV infection. However, the possible pathomechanism of EPF has gradually been elucidated in recent days.

As for the mechanism of eosinophilic accumulation to hair follicles, it has been reported that eosinophilic chemotactic factor was found in skin surface lipid products[12], which seems to be a reasonable explanation because most of the EPF lesions are distributed in seborrheic region of the patients with the past history of acne.

Since the clinical features of EPF resemble dermatophyte and/or *Malassezia* folliculitis, it is speculated that some unknown reactions may occur to these infectious microorganisms, though the pustules in EPF are definitely sterile. A favorable response to antifungal therapy in some cases may support this concept[13].

Elicitation of follicular inflammation by eosinophils can be attributable to eosinophilic cationic protein[14] and nitric oxide[15], which may provide a novel treatment tool for EPF by regulating these inflammatory factors.

Peripheral eosinophilia can partly be explained by micro environmental change of cytokines such as IL-5, because peripheral eosinophilia was observed in EPF patients with myelodysplastic syndrome[16] and drug-induced EPF[17]. The periodical flare up of EPF lesions may be partly due to the fluctuation of cytokine levels in view of interferon studies[18,19].

Most of the immunosuppression-associated EPF is seen in patients with AIDS, which shows both common and different features of classic EPF. It is reported that eotaxin-1 and Th2 cytokines play a crucial role in eosinophil recruitment and inflammation leading to the tissue injury of hair follicles[20]. Since immunosuppression-associated EPF can be found in patients with other hematologic malignancy such as lymphoma and leukemia, some common immunological impairment induced by whatever stimuli may be involved in the pathogenesis of EPF. In immunosuppression-associated EPF, superficial fungal infections are suspected to participate[21,22] because EPF displays similarities with dermatophyte folliculitis, however, no direct evidence supports this concept.

Infancy-associated EPF which is usually found in the scalp of children and shows good clinical response to corticosteroids[23-25], may be somewhat different from adult EPF but a variety of skin diseases such as scabies, insect bites and linear IgA-dermatosis though histopathology bears a close resemblance[26].

Clinical manifestations and laboratory findings

Classic EPF occurs predominantly in middle-aged men, which affects face, trunk and arms. Characteristic features of classic EPF are pruritic follicular papules and sterile pustules which enlarge gradually making a well demarcated area (Fig. 2a). There is a central healing tendency leaving slightly scaly pigmentation (Fig. 2b). On face, slightly elevated maculoerythematous indurations with scattered papules and pustules are occasionally seen, which subside

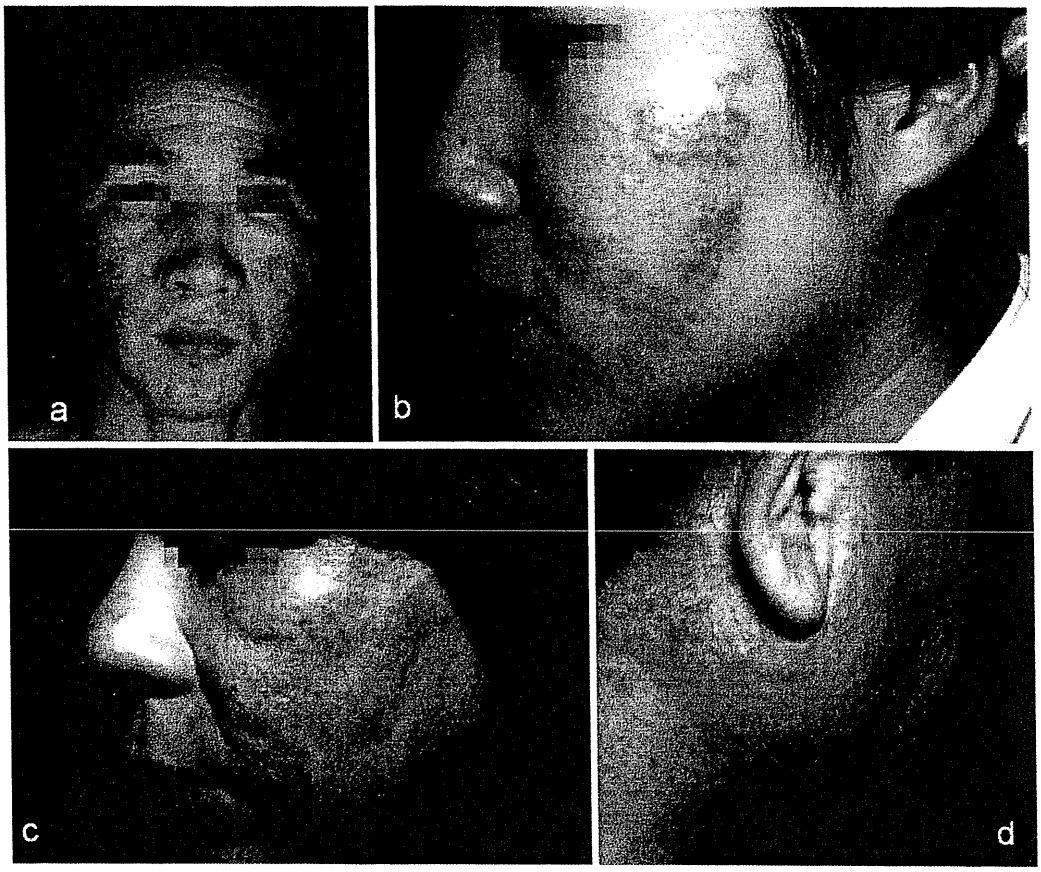

Fig. 2. Clinical features of eosinophilic pustular folliculitis. (a) Characteristic features of classic EPF are pruritic follicular papules and sterile pustules which enlarge gradually making a well demarcated area. (b) There is a central healing tendency leaving slightly scaly pigmentation. (c, d) On face, slightly elevated maculoerythematous indurations with scattered papules and pustules are occasionally seen, which subside spontaneously in due course but flare up periodically resulting in a chronic course.

spontaneously in due course but flare up periodically resulting in a chronic course (Fig. 2c, d). When palmoplantar regions are involved, symmetrical erythema and pustules resembling palmoplantar pustulosis are observed with hypertrophic scaling. Over half patients complain of itching. Usually there is no prodrome or systemic symptoms noticed. Differential diagnosis of classic EPF includes inflammatory acne, rosacea, tinea corporis, pustular psoriasis, subcorneal pustular dermatosis and seborrheic dermatitis.

Mild to moderate eosinophilia is occasionally observed with elevated IgE level. Since EPF is occasionally accompanied with HIV infections and other immunosuppressive conditions such as hematologic malignancies, these complications should be carefully checked.

Histopathology

Immunosuppression-associated EPF and infancy-associated EPF are indistinguishable histologically from classic EPF regardless of their different clinical features. The histopathology of typical EPF is characterized by a dense inflammatory infiltrate of mononuclear cells and eosinophils around hair follicles and sebaceous glands (Fig. 3a). In early phase papular eruption, spongiosis of the outer root sheath of the follicles presumably due to the destruction mediated by eosinophils is observed (Fig. 3b).

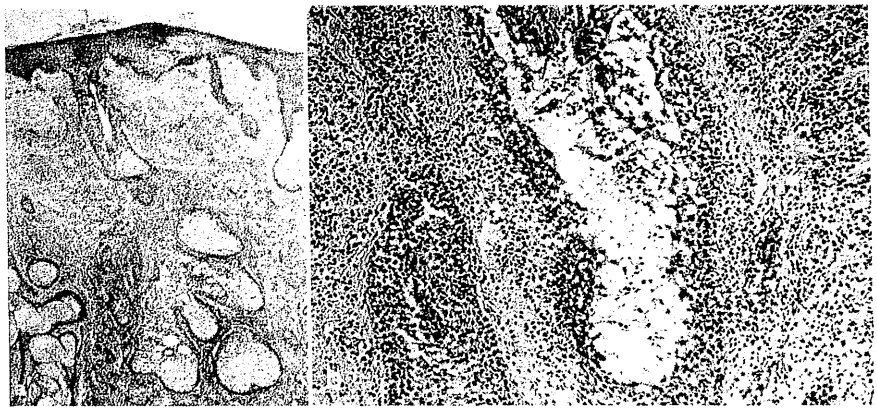

Fig. 3. (a) The histopathology of typical EPF is characterized by a dense inflammatory infiltrate of mononuclear cells and eosinophils around hair follicles and sebaceous glands. (b) In early phase papular eruption, spongiosis of the outer root sheath of the follicles presumably due to the destruction mediated by eosinophils is observed.

In advanced stage, eosinophilic infiltration extends to the whole hair follicles leading to the pustular formation. Mucinous degeneration of the sebaceous gland and outer root sheath may be seen. Moderate increases of tryptase-positive and chymase-negative mucous type mast cells are observed which might play some role in the pathogenesis[27]. Electron microscopic observation revealed that T cells may be involved in the pathomechanism of EPF[28]. As for the infancy-associated EPF, it is speculated that this type of EPF is not a distinctive inflammatory disease of the skin but a variety of different diseases, and the term "eosinophilic folliculitis" is better defined as a histopathologic pattern for infancy-associated EPF[29].

Treatment

Various treatments have been proposed for EPF, however, the endpoint of the treatment should be to control the disease with mild side effects, since EPF shows a chronic course with wax and wane. Topical corticosteroids might be the first choice of the drug, but the clinical effect is sometimes limited. Among other treatment options such as phototherapy[30], systemic steroids, dapsone[31], metronidazole[32], minocycline and retinoids, oral indomethacin seems to be the most promising choice of the treatment[33,34]. Topical indomethacin is also effective in some cases[35]. The mechanism of action by which indomethacin works on EPF still remains unclear, however, indomethacin either suppresses the production of cyclooxygenase-dependent eosinophilic chemotactic factor or alters the cytokine balance leading to the inhibition of prostanoids synthesis[18].

Recently, in addition to indomethacin, other treatments have been applied for EPF[36]. Oral cyclosporine[37] and topical tacrolimus[38] may be beneficial choices when patients have been resistant to previous conventional treatments. Tacrolimus may act against EPF presumably through the inhibition of several proinflammatory cytokines by T cells as well as the prevention of the cytokine release from mast cells[39].

Prognosis of EPF is relatively poor resulting in chronic course with the remission and relapsing for years in many patients.

Conclusion

EPF was first described by an Asian dermatologist as a noninfectious inflammatory skin disease characterized by eosinophilic infiltration mainly of hair follicles, which revealed later as a globally important skin disease because immunosuppression-associated EPF was recognized as an HIV-related skin disease. EPF may be induced by whatever

antigenic stimuli and some unknown immunological reaction patterns with eosinophil participation mainly in the hair follicles may be involved. Development of a new treatment may reveal not only the pathomechanism of EPF but also some hidden multifactorial immune responses in skin diseases mediated by cytokines and chemokines for eosinophils.

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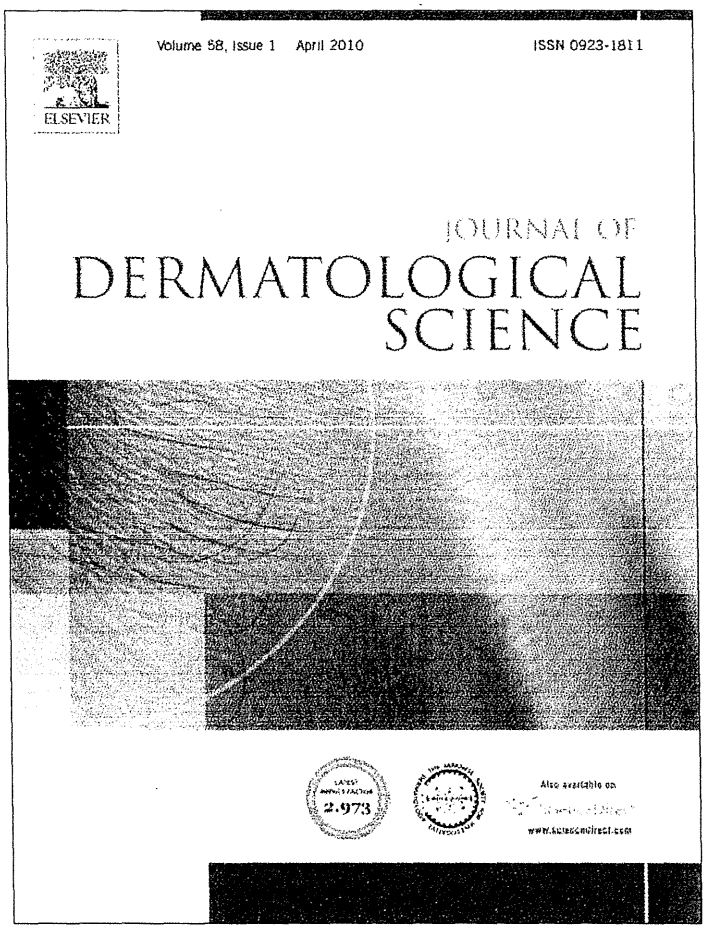

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Invited review article

Extrinsic and intrinsic types of atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) can be categorized into the extrinsic and intrinsic types. Extrinsic or allergic AD shows high total serum IgE levels and the presence of specific IgE for environmental and food allergens, whereas intrinsic or non-allergic AD exhibits normal total IgE values and the absence of specific IgE. While extrinsic AD is the classical type with high prevalence, the incidence of intrinsic AD is approximately 20% with female predominance. The clinical features of intrinsic AD include relative late onset, milder severity, and Dennie-Morgan folds, but no ichthyosis vulgris or palmar hyperlinearity. The skin barrier is perturbed in the extrinsic, but not intrinsic type. Filaggrin gene mutations are not a feature of intrinsic AD. The intrinsic type is immunologically characterized by the lower expression of interleukin (IL)-4, IL-5, and IL-13, and the higher expression of interferon-γ. It is suggested that intrinsic AD patients are not sensitized with protein allergens, which induce Th2 responses, but with other antigens, and metals might be one of the candidates of such antigens.

Contents

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1. History of extrinsic and intrinsic atopic dermatitis (AD)

AD is a clinically defined, chronic-intermittent, genetically predisposed, eczematous dermatitis that starts at infancy or early childhood. Although a large number of clinical, laboratory and experimental studies have been performed, the pathophysiology of AD remains to be elucidated, because AD has a variety of aspects in the causes and pathogenesis.

The clinical phenotype of AD has been classified into the extrinsic and intrinsic types [1]. Historically, this dichotomy was first used for asthma. The terminology of extrinsic or allergic asthma was first introduced by Rackeman in 1947 and referred to the triggering role of allergens in asthma. By symmetry, he described intrinsic or non-allergic asthma as a disease characterized by later onset in life, female predominance, higher degree of severity, and more frequent association with nasosinusal polyposis. As intrinsic asthmatic patients was not improved by conventional treatments, this author considered intrinsic asthma to be caused by a non-allergic, unknown phenomenon [2].

In AD, the extrinsic and intrinsic types began to be adopted in the late 1980s [3]. They are also called the allergic (or classical) and non-allergic types. Since there is still no sufficient consensus whether the intrinsic type is a distinct entity, some researchers denominate it atopiform dermatitis [4]. However, the classification into the extrinsic and intrinsic AD has been widely used especially since the millennium. Recently, various kinds of clinical studies have been performed under this dichotomy in many countries, including Germany [1,5,6], Netherland [4], Hungary [7], Italy [8,9] and other European countries, and Asian countries such as Korea [10,11], and Japan [12].

2. Definition

Extrinsic AD and intrinsic AD are defined according to IgE-mediated sensitization, namely the presence or absence of specific IgE for environmental allergens and food allergens [11,12,13]. According to the EAACI nomenclature task force, the term "atopic eczema/dermatitis syndrome (AEDS)" can be used to cover the different subtypes of AD. In this nomenclature, the intrinsic type is termed non-allergic AEDS, which shows normal IgE levels, no specific IgE, no association with respiratory diseases (bronchial asthma or allergic rhinitis), and negative skin-prick tests to common aeroallergens or food allergens [14]. Since total serum IgE values are significantly associated with the allergen-specific IgE status [15], total IgE can be regarded as a clinically useful parameter to differentiate between the extrinsic and intrinsic types in both adults [5,12] and children [15]. The reported mean values of total serum IgE in the intrinsic type are from 22.2 to 134 kU/l, or alternatively, IgE values less than 150 or 200 kU/l have been used for an indication of intrinsic AD [16]. Our study of Japanese patients also showed that the mean value of total serum IgE was 110.5 kU/l (11–219 kU/l) [12].

Among specific IgE antibodies, infantile AD patients are more allergic to food [11], while environmental antigens are common in adults. It should be careful that some allergens may not be useful to discriminate the two types. For example, IgE to *Malassezia sympodialis* was found in patients with the intrinsic type as well as the extrinsic type [17].

3. Prevalence of intrinsic AD

3.1. Incidence

Since extrinsic AD is the prototype of AD, its prevalence is well known. On the other hand, the frequency of intrinsic AD has been a matter of investigation. Schmid et al. [16] summarized the twelve reports that has been published from 1990 to 2000 and documented the clinical features of extrinsic and intrinsic AD. According to their review paper, the frequency of intrinsic AD was 10–45%. More recently, the incidence of extrinsic AD and intrinsic AD were reported as follows: 73% *vs* 27% [18] and 63% *vs* 37% [15] in German children, 88% *vs* 12% in Hungarian adults [7], 78.2% *vs* 21.8% in Dutch patients from 13 to 37 years of age [4], and approximately 80% *vs* 20% in Korean [19]. These data are in accordance with the empirical knowledge that about 20% of AD patients show normal IgE levels and lack of sensitization towards environmental allergens. Intrinsic AD is seen in various countries, but the prevalence may depend on local areas, as it was reported that intrinsic AD was higher in incidence in East Germany than West Germany, although the exact reason remains unclear [6].

3.2. Female predominance

The female predominance in intrinsic AD is well known and has been observed by a number of studies [1,4,16,20]. Our observation disclosed that 76.5% of AD patients were female [12]. More extremely, the 14 intrinsic AD patients enrolled in a study by another group were all female [20].

3.3. Adults and children

Several reports on the prevalence may provide an implication that the intrinsic type is seen at higher frequencies in children than adults [15]. A Korean group of AD investigators showed that the intrinsic type is more prevalent in infancy, and even the third group of the indeterminate type between the intrinsic and extrinsic ones can be identified in this younger generation [11]. A prospective birth cohort study followed for 5 years by a German group demonstrated that one third of child AD was the intrinsic one, and more common in female [21]. Another German group indicated the low prevalence of the intrinsic AD among adult patients [5]. They showed 6.9% patients fulfilled the criteria of intrinsic AD, and after follow-up, the incidence was declined to 5.4% because some patients developed respiratory allergies or IgE-mediated sensitizations. Taken together these observations, it is likely that the intrinsic type is more prevalent in children than adults.

4. Clinical features

The skin manifestations of the two types of AD are indistinguishable. As shown in Figs. 1–3, patients with the intrinsic type share the features with those with extrinsic type. However, Brenninkmeijer et al extensively studied the clinical features of intrinsic AD [4] and found that the Dennie-Morgan fold is significantly more present in the intrinsic type (Fig. 2). The later onset of disease and milder

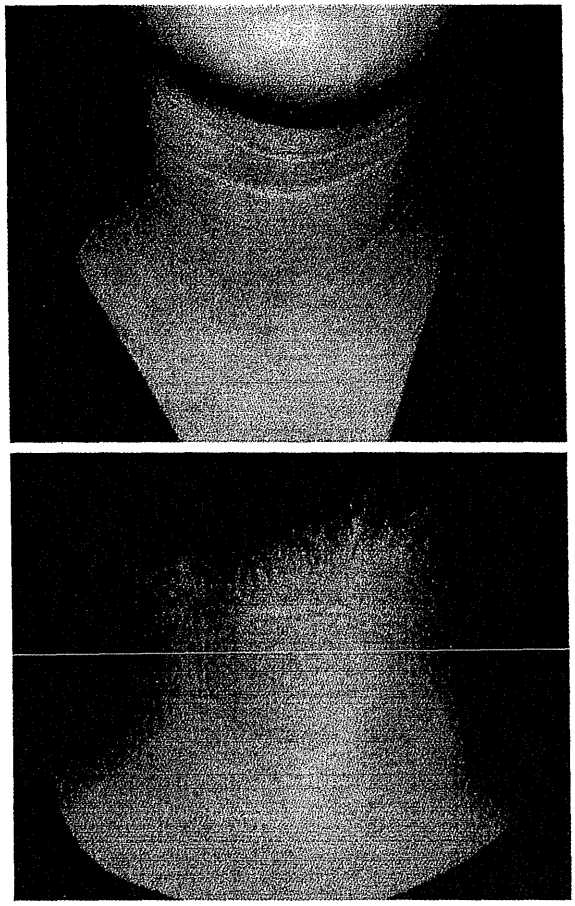

Fig. 1. Intrinsic AD. A 25-year-old female, with total serum IgE, 69 kU/l; and blood eosinophils, 10%. A lichenified eruption on the neck and upper chest (top) and nuchal area (bottom).

disease severity are also characteristics of intrinsic AD. The features that are negatively associated with intrinsic AD include personal or family history of atopy, recurrent conjunctivitis, palmar hyperlinearity, keratosis pilaris, pityriasis alba, non-specific hand or foot eczema, and influence of emotional or environmental factors [4]. As mentioned below, some of these non-associated features are considered to stem from the lack of barrier disruption and/or filaggrin gene mutations in intrinsic AD (Table 1).

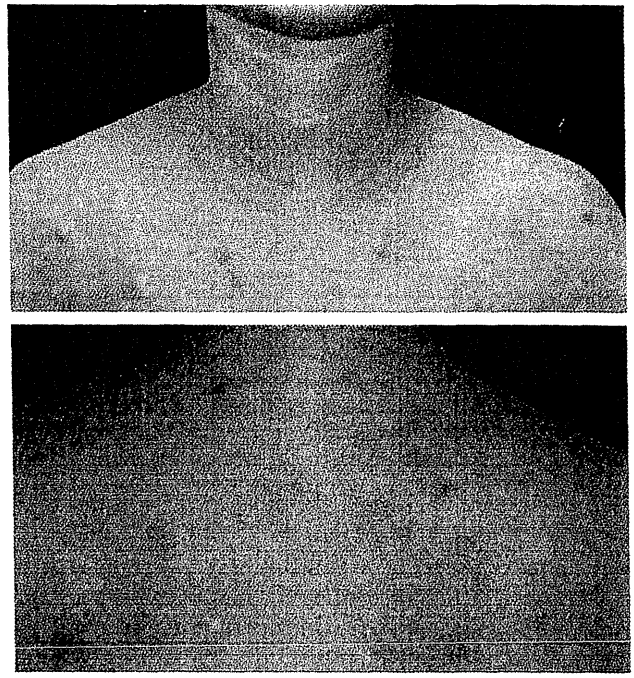

Fig. 3. Intrinsic AD. A 29-year-old female, with total serum IgE, 43 kU/l; and blood eosinophils, 11%. A lichenified eruption on the neck and upper chest (top) and upper back with scratches (bottom).

5. Skin barrier function

5.1. Barrier function of stratum corneum

The barrier function is usually assessed by transepidermal water loss (TEWL) and skin surface hydration (capacitance). The extrinsic AD patients showed increased TEWL and lower skin surface hydration, whereas the intrinsic patients showed no significant differences in TEWL or skin surface hydration as compared to control [19]. On the antecubital fossae, both types of AD patients showed higher TEWL and decreased capacitance. We examined the skin surface hydration and TEWL at the nonlesional forearm and lower leg of patients and normal volunteers in a comparison between the extrinsic and intrinsic types [12]. The level of skin surface hydration was significantly lower in extrinsic AD than in normal control subjects. On the other hand, there was

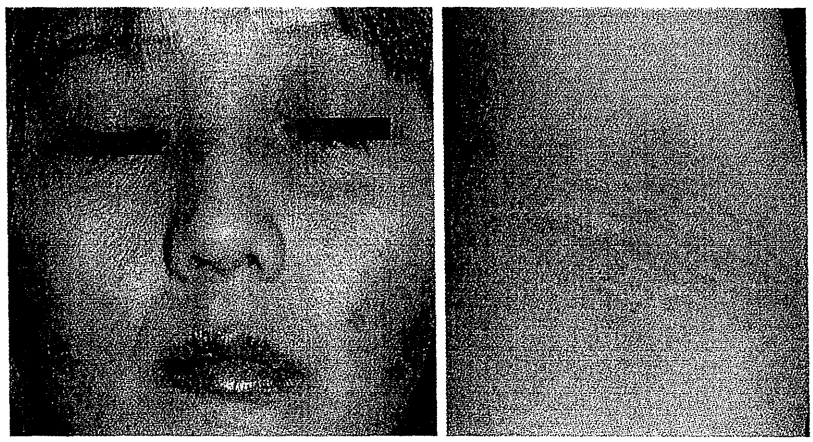

Fig. 2. Intrinsic AD. A 32-year-old female, with total serum IgE, 226 kU/l; and blood eosinophils, 18%. A lichenified eruption with Dennie-Morgan folds on the lower eyelids and pigmentation on the lips (left); and a pigmented and chronic lesion on the antecubital fossa (right).

Table 1
Characteristics of intrinsic AD.

1. Definition
Normal total serum IgE values (mean total serum IgE, 22.2–134 kU/l [1])
Absence of specific IgE for environmental allergens and food allergens
2. Incidence
Percentage of intrinsic AD in total AD: 10–45% [1], 27% [2], 37% [3], 12% [4], 21.8% [5], 20% [6]
Female predominance (collectively 70–80%) [1,5,7,8]
3. Clinical features
Dennie-Morgan fold [5]
No ichthyosis vulgris or palmar hyperlinearity [5]
No non-specific hand or foot eczema [5]
Lower colonization of *Staphylococcus aureus* [9]
Relative late onset
Milder severity
4. Skin barrier
Normal barrier function [6,10]
No filaggrin mutation (presence of filaggrin mutations in extrinsic AD [24,25])
5. Immunological features
Lower expression of IL-4, IL-5, and IL-13 [11]
Higher expression of IFN-γ [12]
6. Contact allergens
High prevalence of metal allergy [39,40]

no significant difference in the hydration level between intrinsic AD and healthy control. The extrinsic type tended to be lower than the intrinsic type at both sites. Thus, the skin barrier function was impaired in extrinsic AD and preserved in intrinsic AD.

5.2. Pruritus perception and barrier function

The skin perception threshold of electric current stimuli is one of the indices of itch. We found that the electric current perception threshold was significantly correlated with the skin surface hydration and inversely with TEWL in intrinsic AD patients as well as healthy individuals. In contrast, extrinsic AD patients did not exhibit such a correlation. Therefore, intrinsic AD patients retain the normal barrier function and sensory reactivity to external pruritic stimuli [14].

5.3. Presence and lack of filaggrin mutations in extrinsic and intrinsic AD, respectively

The recent identification of loss-of-function mutations in filaggrin as a widely replicated major risk factor for eczema sheds new light on the mechanisms of AD [22].

These mutations also represent a strong genetic predisposing factor for atopic eczema, asthma and allergies in various countries [23]. Profilaggrin is the major component of the keratohyalin granules within epidermal granular cells. During epidermal terminal differentiation, the profilaggrin polyprotein is dephosphorylated and rapidly cleaved by serine proteases to form monomeric filaggrin, which is further degradated into natural moisturising factor. Recent human genetic studies strongly suggest that perturbation of skin barrier function as a result of reduction or complete loss of filaggrin expression leads to enhanced percutaneous transfer of allergens. Filaggrin is therefore in the frontline of defense, and protects the body from the entry of foreign environmental substances that can otherwise trigger aberrant immune responses. The association of the filaggrin mutations in particular with the extrinsic type of AD was observed [24,25]. Furthermore, filaggrin mutations are significantly associated with palmar hyperlinearity in patients with AD, which represents a shared feature of AD and ichthyosis vulgaris. This is in accordance with the finding that palmar hyperlinearity is negatively associated in the intrinsic type [4]. In our preliminary study, we found that typical cases of intrinsic AD had no mutation in filaggrin, whereas some of the extrinsic patients possessed filaggrin mutations. Although future studies are necessary, it is expected that barrier disruption, as represented by filaggrin gene mutations, is associated with extrinsic AD.

6. Immunological characteristics of circulating T cells and cytokines/chemokines

6.1. Systemic Th1/Th2 immunological state

AD is well known as a Th2-polarized disease. However, there have been reported some differences in systemic cytokine polarization between the two types of AD. As expected with elevation of total serum IgE, extrinsic AD patients show high levels of Th2 cytokines, IL-4, IL-5 and IL-13, and intrinsic AD is linked with much lower levels of IL-4 and IL-13 [8]. Along with the elevation of IL-5 [26,27], eosinophil counts [11] and eosinophil cationic protein levels [18] are increased in the extrinsic type of AD. On the other hand, there was a report demonstrating that both extrinsic and intrinsic patients showed increased production of IL-5 and IL-13 [28]. In that study, however, when peripheral blood mononuclear cells were stimulated with anti-CD3 antibody, extrinsic AD patients had a decreased capacity to produce IFN-γ and GM-CSF as compared to the intrinsic AD [28]. Accordingly, we found, in our preliminary study, that there was no significant difference in the percentages of $IL\text{-}4^+$ or $IL\text{-}17^+$ T cells between the extrinsic and intrinsic types, but that of $IFN\text{-}\gamma^+$ T cells was higher in the intrinsic type than the extrinsic type. Thus, there are some variations in these results of Th1 and Th2 cytokines, perhaps depending on the evaluation systems, i.e., measurements of cytokine protein amounts in either *in vivo* sera or *in vitro* culture supernatants, mRNA expression by lymphocytes, and intracellular cytokine staining in T cells. However, all the data can be interpreted to indicate that the extrinsic pathogenetic factors mount a Th2-skewing action, and that the intrinsic type shows less Th2-skewing state or relative overproduction of Th1 cytokine IFN-γ.

6.2. Chemokines and others

With regard to chemokines, patients of both types showed high serum amounts of CCL17/TARC and CCL22/MDC and high peripheral blood mononuclear cell expression of CCL17 and CCL22 at comparable levels [29]. Therefore, no difference was observed in the promoted production of chemokines attractive to Th2 cells. The blood levels of soluble receptors derived from lymphocytes correlate to the activity in various diseases. There is no significant difference in the elevated amounts of sCD23, sCD25, and sCD30 between the two types [30].

7. Immunological characteristics of skin lesions

7.1. T cells and cytokines

In skin lesions, $CD4^+$ T cells, $CD8^+$ T cells, and Langerhans cells are comparably increased in both extrinsic and intrinsic AD, but eosinophils infiltrate in the dermis more markedly in the extrinsic than the intrinsic type, and the extrinsic type exhibits more prominent deposition of eosinophil granular protein and higher staining for eotaxin [10,31]. Although the levels of mRNA expression for IL-5, IL-13, and IL-1β are higher in both types of AD patients than non-atopic subjects, extrinsic AD shows even higher levels than intrinsic AD [31]. The expression of IFN-γ, IL-12, and GM-CSF, IL-4, and IL-10 are elevated in both types without

differences between the extrinsic and intrinsic AD [31]. Thus, tissue eosinophilia and IL-5 expression may be a characteristic of the extrinsic type.

7.2. Dendritic cells (DC) and Langerhans cells (LC)

As to epidermal DC, the extrinsic type is characterized by a significantly high level of the expression of IgE high-affinity receptor (FCεR) on the $CD1a^+$ epidermal DC compared to the intrinsic type [1,32]. When the high-affinity/low-affinity expression ratio is used as a disease marker for AD, the values for intrinsic AD fall below the diagnostic cut-off level, suggesting that intrinsic AD can be distinguished by phenotyping of epidermal DC [1,32]. In accordance with these data from the lesional skin, the surface expression of the high- and low-affinity receptor for IgE and the IL-4Rα chain are significantly elevated in monocytes from patients with the extrinsic type [2]. As described below, it is possible that epidermal LC in the barrier-disrupted skin produce high amounts of Th2 and eosinophil chemokines, further suggesting that LC are activated in the extrinsic type.

8. Relationship between barrier status and skin immune reactions

8.1. Epidermal cytokine production in barrier-disrupted skin

The skin immune status is closely associated with the disordered condition of skin barrier (Fig. 4). Studies using a mouse model of contact hypersensitivity (CHS) have shown that CHS responses to hapten are increased when a hapten is applied to the barrier-damaged skin [33]. Barrier disruption of the skin is experimentally performed by extraction of epidermal lipids with acetone or removal of corneocytes by tape stripping. Both procedures can induce elevated CHS responses. Not only increased permeability of hapten through the epidermis but also altered immune functions of epidermal cells potentiate T-cell activation in acute barrier disruption [33]. Such augmentation of immune reactivity may be critical to elimination of environmental noxious agents that penetrate easily into the barrier-disrupted epidermis, and it is also closely related to the mechanism underlying extrinsic AD.

8.2. Epidermal chemokine production in barrier-disrupted skin

Regarding epidermal chemokines of the barrier-disrupted skin, the mRNA expression levels of Th1 chemokines (CXCL10, CXCL9 and CXCL11), Th2 chemokines (CCL17 and CCL22) and eosinophil chemoattractant (CCL5) are high in the epidermal cells from BALB/c mice. In particular, we found that CCL17, CCL22 and CCL5 were remarkably elevated in BALB/c mice [34]. Tape stripping induced dermal infiltration of eosinophils in BALB/c mice, and the late-phase reaction was increased with infiltration of Th2 cells as well as eosinophils, when challenged *via* the tape-stripped skin. Notably, Th1 chemokines (CXCL9 and CXCL10) and Th2 chemokines (CCL17 and CCL22) are derived mainly from keratinocytes and LC, respectively [35]. In this notion, one of the crucial actions of IFN-γ is upregulation of keratinocyte production of Th1 chemokines and downregulation of LC production of Th2 chemokines. Therefore, the barrier damage likely induces the infiltrates of Th2 cells and eosinophils in extrinsic AD, but their infiltrates are inhibited by IFN-γ in intrinsic AD.

8.3. Implications for the difference between extrinsic and intrinsic AD

The above findings suggest that Th2 and eosinophil responses and resultant late-phase reaction are prone to take place in the skin with damaged barrier by the modulated function of LC. This may provide the mechanism of Th2-polarized immunophenotype of the extrinsic AD. On the contrary, LC are not stimulated to produce Th2 chemokines in the intrinsic type because of the presence of normal stratum corneum. Protein antigens penetrating the damaged barrier further induce the Th2-shifted response in the extrinsic AD, while non-protein antigens exert the Th1 response as well in the intrinsic AD (Fig. 4).

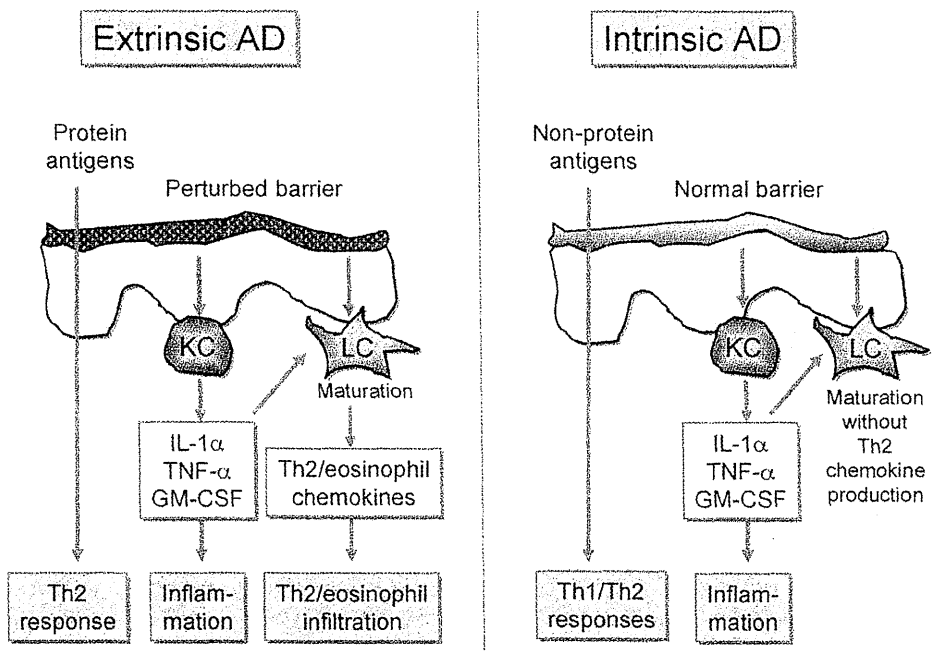

Fig. 4. Comparison between extrinsic and intrinsic AD in relation to the barrier and immune states.
Protein and non-protein antigens are causative in the extrinsic and intrinsic types, respectively. In both types, antigen application to the skin stimulates keratinocytes to produce cytokines, including IL-1α, TNF-α, and GM-CSF, which induce maturation of Langerhans cells (LC). In the perturbed skin of extrinsic AD, LC can produce CCL17/TARC, CCL22/MDC, and CCL5/RANTES, which promote infiltration of Th2 cells and eosinophils. On the other hand, LC of the intrinsic AD do not elaborate those chemokines.

It has been reported that Th2 cytokine IL-4 suppresses the enhancement of ceramide synthesis and cutaneous permeability barrier functions, which further aggravates the barrier [36]. This 'outside-to-inside, back to outside' paradigm [37] is applicable for the pathogenesis of extrinsic AD. A more recent observation suggests that neutralization of the normally acidic stratum corneum has deleterious consequences for permeability barrier homeostasis and stratum corneum integrity/cohesion attributable to serine proteases activation leading to deactivation/degradation of lipid-processing enzymes and corneodesmosomes [38]. Hyperacidification improves permeability barrier homeostasis, attributable to increased activities of two key membrane-localized, ceramide-generating hydrolytic enzymes, which correlate with accelerated extracellular maturation of stratum corneum lamellar membranes. Thus, the surface pH may be another important factor to differentiate between the extrinsic and intrinsic types.

9. Patch tests and metal allergy

9.1. Patch tests for mite antigens

An Italian group performed patch test with house dust mites at a concentration of 20% in petrolatum in the extrinsic and intrinsic types of adult male AD patients [9]. The patch test was positive in 47.4% of extrinsic AD and in 66.6% of intrinsic AD, and in 12.2% of healthy subjects [9]. Since that extrinsic AD patients usually have high levels of IgE specific for mites, the authors wondered the reason why the patch test was highly positive in the intrinsic AD. However, patch tests can reflect mostly the T-cell mediated contact sensitivity, and the IgE-high extrinsic nature does not promote the patch test reactions. Rather, given that IFN-γ is produced at a higher level in the intrinsic type than the extrinsic type, the higher frequency of positive reaction in the intrinsic type seems to be reasonable.

9.2. Patch tests for metals

It is known in patients with AD that the most frequent contact allergens are metals [39]. In 137 atopic children, 19.3% patients were positive to metals [39]. In 1965, Shanon reported that patients with metal allergy occasionally exhibit a skin manifestation indistinguishable from AD under the name of "pseudo-atopic dermatitis" [40,41], and chrome is the causative in their report [40]. Some patients with AD were improved by intake of metal-free diet and elimination of metals [41]. We found that patients with intrinsic AD showed positive patch tests to cobalt, chrome, and/or nickel at a higher percentage than extrinsic one, suggesting that systemic metal allergy is one of the potential causes of intrinsic AD. With regard to metals, our tentative observation with sweat demonstrated that a high incidence of sweat allergy in AD and a therapeutic effect of desensitization with sweat in the patients. Since sweat contains high concentrations of metals, this finding might be related to the pathogenetic role of metals in intrinsic AD.

10. Skin infections

Both extrinsic and intrinsic AD patients suffer from recurrent bacteria and viral infections [42]. A higher colonization of *Staphylococcus aureus* was observed in the extrinsic (71%) *vs* the intrinsic children (49%) [43]. The expression of human β-defensin-3, an anti-microbial peptide, is decreased in both types of AD as compared to normal skin and psoriatic skin [42]. Therefore, skin infection with microorganisms, in particular *S. aureus*, may be severer in the extrinsic type because of barrier perturbation, but it remains unclear whether or not the defense responses are different between the types.

11. Neurotrophins and neuropeptides

Neurotrophins, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are increased in both extrinsic and intrinsic AD, suggesting a similar pathophysiologic background implicating a neuroimmune network [27]. However, there is a significant correlation between BDNF and SCORAD only in the intrinsic type [27]. Maternal NGF levels were significantly higher in patients with both extrinsic and intrinsic AD than controls [30]. It is an issue to be elucidated whether these neurotrophines or neuropeptides such as substance P are different between the two types.

12. Animal models for intrinsic AD

A non-IgE-associated AD model was regarded as a mode of human intrinsic AD [44]. In an animal model of AD, IL-18 contributes the spontaneous development of AD-like skin lesions independently of IgE [45]. When the skin barrier was destroyed in mice and protein A from *S. aureus* was topically applied to the skin, the mice developed AD lesions with dermal infiltration of eosinophils and mast cells and showed an increase in serum levels of IL-18, but not IgE [46]. In this model, IL-18 might be important for the development of infection-associated AD by induction of IL-3 from IFN-γ- and IL-13-producing "super" Th1 cells. Since the intrinsic AD shows high levels of IFN-γ-producing cells [28] and normal levels of IgE, this mouse model resembles intrinsic AD and suggests that some intrinsic AD patients may be related to infection.

13. Conclusions

The causes and mechanisms of intrinsic AD remain unfully elucidated. However, as compared to extrinsic AD, the intrinsic type can be characterized by normal barrier function [12] and IFN-γ-producing potency [28]. These findings suggest that the intrinsic AD patients are not sensitized with protein allergens, which induce Th2 responses, but with other antigens. Metals might be one of the candidates as antigens [40].

Some dermatologists are still skeptical whether the distinction between the intrinsic and extrinsic types of AD is really meaningful. If the contactants and pathophysiology of intrinsic AD are clarified, we might eliminate the term of "intrinsic" from the whole spectrum of AD. However, we have been unable to elucidate them to date. Furthermore, as shown in Figs. 1–3, the clinical appearance of intrinsic AD resembles that of extrinsic AD, expect for a small group of intrinsic patients. In this context, it is reasonable to use "intrinsic" in clinical dermatology.

The extrinsic nature may be changed as the patients grow. Therefore, the classification into the extrinsic and intrinsic types is necessary at each stage of life, i.e., infancy, childhood, teenage, and adult for the allergological management of patients as to allergen avoidance, second allergy prevention, and immunotherapy [14]. However, the risk of an "atopy march" is significantly lower in children with the intrinsic type [14].

A German study demonstrated that the intrinsic type was associated with early daycare attendance [21]. In relation to the feasibility of AD in individuals, early daycare attendance is known as a factor related to the hygiene hypothesis as well as the number of older siblings of individuals. Therefore, intrinsic AD is different from extrinsic AD, whose development is depressed by Th1-inducing environmental factors. Again, it appears that the intrinsic type is not related to the pure Th2 dominant immunological state. Future studies on the intrinsic type of AD may clarify the pathophysiology of not only intrinsic AD, but also dermatitis of

unknown cause that have been called atopiform dermatitis [4] or pseudo-atopic dermatitis [40].

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The Mandatory Role of IL-10–Producing and OX40 Ligand-Expressing Mature Langerhans Cells in Local UVB-Induced Immunosuppression

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