



REVIEW ARTICLE

Atopic dermatitis in older adults: A viewpoint from geriatric dermatology

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Atopic dermatitis (AD) in older adults represents a newly defined subgroup of AD. The prevalence of elderly AD is approximately 1–3% among elderly populations in industrialized countries. Elderly patients with AD show some common clinical characteristics, such as a male predominance, a lower incidence of lichenified eczema at the elbow and knee folds, and particular patterns of onset and clinical course. Both immunoglobulin (Ig)E-allergic and non-IgE-allergic types are observed in elderly AD. Elderly patients with IgE-allergic AD show high rates of positivity for specific IgE antibodies against house dust mites, associations with IgE allergic and asthmatic complications, histopathological features with a predominance of IgE-mediated allergic inflammation in the lesional skin, and a significantly lower incidence of malignancy as compared with control subjects. The etiology of elderly AD might be associated with immunosenescence, age-related changes to the sex hormone milieu, age-related barrier dysfunctions in the skin and gut, functional disturbance of sweat production, and environmental stimuli in the lifestyle of elderly individuals. Powerful anti-inflammatory treatments, such as oral corticosteroids, might be required together with standard treatments to manage moderate to severe cases of elderly AD. Finally, most elderly patients with AD reach the end of life with this disease, which should now be considered a lifelong allergic disease. **Geriatr Gerontol Int 2016; 16 (Suppl. 1): 75–86.**

Keywords: clinical characteristics, immunoglobulin E, management, prognosis, skin manifestations.

Introduction

Atopic dermatitis (AD; also known as atopic eczema) is a chronic, relapsing skin disease manifesting as dry skin, persistent itching and various forms of eczematous dermatitis, and characterized by a pathogenesis involving allergic inflammation and skin barrier defects.^{1,2} AD was added to the group of atopic disorders in the 1930s based on the association with other atopic diseases, such as bronchial asthma (BA) and allergic rhinoconjunctivitis (AR), and the characteristic of specific skin hypersensitivity to environmental (including food) allergens.³ Before the 1960s to 1970s, AD was basically considered a pediatric disease with good prognosis (known as classic childhood AD), as the pathology

mostly appeared in infancy or childhood and typically resolved before or shortly after puberty. Although a small number of cases with prolongation of the disease course until young adult life (i.e. adult AD) had also been reported in the 1930s, AD in middle age was considered extremely rare, and no typical case of AD over 50 years-of-age was observed.³ From the 1980s, with the increasing incidence of childhood AD seen in industrialized and civilized society, cases of AD either persisting or first appearing in adolescence, young adulthood, or the subsequent late adult phase increased, and were termed adult-type AD.⁴ Recently, cases of AD manifesting in the senile phase (i.e. elderly AD) have gradually been increasing with the aging of society, allowing for characterization of the clinical and histopathological features.^{5–9} As a result, a recent edition of a textbook on dermatology divided AD into four phases: infantile (age <2 years); childhood (age 2–12 years); adolescent/adult (age >12 years, but <60 years); and elderly (age ≥60 years).¹⁰

The present review focuses on the clinical characteristics, pathophysiology, etiology, management and prognosis of this new subgroup of elderly AD.^{11,12}

Accepted for publication 10 February 2016.

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Clinical characteristics of elderly AD

The characteristics of elderly AD with regard to the following contents are summarized in Table 1.

Epidemiology

The prevalence of AD is lower in older adults than in children and young adults, at 1.86% (age ≥ 60 years)⁷ compared with 5.3% (age 6–12 years) and 3.02% (age 20–44 years)¹³ in Poland, and 2.6% (≥ 60 years)¹⁴ compared with 11.8% (6–7 years)¹⁵ and 9.8% (20–29 years)¹⁶ in Japan. An epidemiological analysis in 2007–2008 reported that 3.39% of patients with AD in Japanese dermatology clinics were elderly (≥ 61 years).¹⁵ A male predominance in elderly AD, especially for the immunoglobulin (Ig)E-allergic type,⁹ was found in studies from Japan^{5,6,14} and Poland.⁷ The male : female ratio in elderly AD was approximately 2:1 in our clinical study of 60 cases,⁹ and 1.75:1 in a study of 121 cases from Poland.⁷ The prevalence of elderly AD in an urban area of Tokyo, Japan, was reported as 3.0% in men and 1.9% in women,¹⁴ and 2.9% in men and 1.1% in women in Poland.⁷

Clinical types

At least two types of AD have been identified: an IgE-allergic type associated with IgE-mediated sensitization to environmental allergens and high levels of total IgE (more than 200 or 400 IU/L) and allergen-specific IgE (positive results in skin prick test and/or serum-specific IgE evaluations); and a non-IgE-allergic type with normal levels of total IgE and a lack of sensitization to environmental allergens.^{17,18} In addition, as is the case with infantile AD,¹⁹ an indeterminate-allergic type also exists in elderly AD with normal levels of total IgE and positivity for allergen-specific IgE or with high levels of total IgE and non-detectable allergen-specific IgEs, and showing an intermediate, vague state between IgE-allergic and non-IgE-allergic types.⁹ In our clinical study of 60 cases (high levels of serum total IgE, >400 IU/L; high levels of serum-specific IgE, positive results in multiple antigen simultaneous test), the frequencies of IgE-allergic type, indeterminate-allergic type, and non-IgE-allergic type in elderly AD were 63.3% ($n = 38$), 15.0% ($n = 9$) and 21.7% ($n = 13$), respectively.⁹ This figure is similar to those observed in childhood and adolescent/adult AD, with IgE-allergic comprising 70–80% and non-IgE-allergic comprising 20–30%^{17,18}.

IgE reactivity and cytokines

Total IgE levels for elderly patients with IgE-allergic AD are mostly within the range of 2500–10 000 IU/mL.^{6,7,9} As for adolescent/adult AD, the most common environ-

mental allergens for IgE-allergic elderly AD are house dust mites (HDM; e.g. *Dermatophagoides* species), followed by pollens (e.g. Japanese cedar and grass pollen). Positive rates were as follows: *Dermatophagoides farinae*, 83.8%; and Japanese cedar, 56.8% in our study,⁹ and *Dermatophagoides pteronyssinus*, 72%; *D. farinae*, 70.9%; and grass pollen, 68.4% in the Polish study.⁷ Positive rates for foods, fungus and animal dander were relatively lower in those studies. Interestingly, Bozek *et al.* reported that elderly patients with low total IgE showed a positive rate of 76% for specific IgE for enterotoxins of *Staphylococcus aureus* (especially for enterotoxins B and D), although these cases appeared to represent non-IgE-allergic AD at first sight because of the absence of sensitization to common environmental allergens.⁷ This 76% positive rate was significantly higher than those in elderly individuals with IgE-allergic AD (29.2%, $P = 0.021$) or in healthy individuals (1%, $P < 0.05$).

Phenotypic analyses of peripheral blood cytokine concentrations in the Polish study showed the dominance of a T-helper (Th)2 cytokine profile; that is, interleukin (IL)-4, IL-5 and IL-13, in elderly patients with IgE-allergic AD, and dominance of a T-helper (Th)1 cytokine profile; that is, IL-2 and interferon- γ , in elderly patients with low total IgE.⁷

Skin manifestations

Skin manifestations in elderly AD basically match those of adult AD, but the reverse sign of lichenified eczema around unaffected folds of the elbows and knees is more common than the classic sign of localized lichenification at those folds.⁴ Chronic eczematous dermatitis on the face and neck, and lichenified/exudative eczematous lesions with or without pruriginous papules and nodules on the trunk and extremities are observed. Other stigmata of AD, such as facial erythema (atopic red face) and pallor, Hertoghe's sign (loss of the lateral eyebrows), Dennie–Morgan infraorbital folds, dirty neck and follicular lichenified papules might also be observed in elderly AD (Fig. 1).^{6–9,11}

Immune pathomechanisms of skin lesions

The pathogenesis of AD is complex. Recent research has provided a new concept beyond the initial Th2/Th1 paradigm, with roles for Th17, Th22, and T-regulatory (Treg) cells, as well as specialized dendritic cells (DC; antigen-presenting cells), mast cells (MC), eosinophils and basophils in the immune pathways of AD.^{2,20,21}

The participation and role of allergen-specific IgE in the development of skin lesions of AD has been controversial, but histopathological analysis in our previous study⁸ showed that, at least in elderly patients with IgE-allergic AD (AD with high levels of total IgE and positivity for allergen-specific IgE), IgE-mediated allergic

Table 1 Clinical characteristics of elderly atopic dermatitis**Epidemiology**

The prevalence of elderly AD is approximately 1–3% in elderly people in industrialized countries^{7,14}

Male predominance: Especially in IgE-allergic elderly AD;⁹ the male : female ratio for elderly AD is approximately 2:1,⁹ 1.75:1⁷

Clinical types

Three types have been categorized: IgE allergic type; non-IgE-allergic type; and indeterminate-allergic type⁹

IgE reactivity and cytokines

Mean total IgE levels of IgE-allergic elderly AD: approximately 2500–10 000 IU/mL^{6,7,9}

Major allergens for IgE-allergic elderly AD: house dust mites (*Dermatophagoides* species) followed by pollens^{7,9}

Dominance of Th2 cytokine profiles; i.e., IL-4, IL-5 and IL-13 in elderly patients with IgE-allergic elderly AD⁷

Dominance of Th1 cytokine profiles; i.e., IL-2 and IFN- γ in elderly patients with low total serum IgE⁷

Skin manifestations

Basically match those of adult AD:

Chronic lichenified eczema with or without pruriginous lesions on the face, neck, trunk and extremities

Other stigma of AD; e.g., atopic red face, Hertoghe's sign, Dennie-Morgan infraorbital folds, dirty neck, etc. are observed

Features of elderly AD that differ from adult AD:

Classic sign of localized lichenification in the folds of the elbows and knees is uncommon

Reverse sign of lichenified eczema around unaffected folds of the elbows and knees is common^{6,9,11}

Immune pathomechanisms of skin lesions

Numerous IgE+ cells; i.e., Langerhans cells, inflammatory DC and MC are found among inflammatory cells infiltrating in IgE-allergic elderly AD

Only a few IgE+ MC are found among inflammatory cells infiltrating in non-IgE-allergic elderly AD⁸

Onset and clinical course

Three main patterns are apparent: geriatric onset (continuous type); geriatric recurrence with history of classic childhood AD (outgrow-recurrence type); continuation and/or recurrence of adult AD (both continuous and outgrow-recurrence types)^{6,9,11}

Complications

Associations with IgE allergic status and asthmatic complications are seen in elderly patients with IgE-allergic AD

Lower incidence of ichthyosis in elderly patients with IgE-allergic AD

Lower incidence of malignancy in elderly patients with IgE-allergic AD⁹

Prognosis

Majority of elderly AD patients show good prognosis after suitable management

Powerful anti-inflammatory treatments, such as oral corticosteroids, are required in moderate to severe cases of elderly AD

Complete remission (outgrowth) rarely arises

Most elderly AD patients will reach the end of life with AD⁹

AD, atopic dermatitis; DC, dendritic cells; IgE, immunoglobulin E; IL, interleukin; IFN- γ , interferon- γ ; MC, mast cells; Th, T-helper.



Figure 1 Skin manifestations of elderly atopic dermatitis. (a) Lichenified eczema around the scarcely involved elbow fold. (b) Localized lichenified eczema in the elbow folds. (c) Diffuse lichenified eczema on the neck and upper back. (d) Facial eczematous erythema (atopic red face) with Hertoghe's sign (loss of lateral eyebrows) and Dennie-Morgan's infraorbital folds. (e) Lichenified eczema on the neck (dirty neck). Figures reproduced with permission from the *Journal of Clinical Medicine*.⁹

inflammation plays a critical role in the features of skin lesions. Immunohistochemical analysis⁸ showed numerous IgE+ cells among inflammatory cells infiltrating into the chronic skin lesions of elderly patients with IgE-allergic AD: IgE+ CD1a+ DC (myeloid DC; mostly Langerhans cells) in the epidermis; IgE+ CD11c+ DC (myeloid DC; inflammatory DC; so-called "atopic" DC)^{22,23} in both the epidermis and upper dermis; and IgE+ MC in the upper dermis. In contrast, although just a few IgE+ MC were detected, no IgE+ CD11c+ cells or IgE+ CD1a+ cells were found in the skin lesions of elderly patients with non-IgE-allergic AD. In control cases, only a few IgE+ MC were observed in non-atopic chronic eczema. In addition, although moderate IgE+ MC and slight IgE+ CD1a+ DC were observed, no IgE+ CD11c+ cells were found in the epidermis or upper dermis in non-eczematous disorders with elevated

serum IgE levels (e.g. cholesterol embolism and Churg-Strauss syndrome) (Fig. 2).^{8,12} The IgE+ CD1a+ DC, IgE+ CD11c+ DC, and IgE+ MC build complexes of IgE and high-affinity receptor FcεRI on the cell surface, and capture large amounts of allergens, leading to allergen-specific inflammatory reactions.^{1,8,22} The IgE-FcεRI-mediated capture of allergens on IgE+ CD1a+ DC and IgE+ CD11c+ DC can lead to efficient presentation of peptides from allergens to naïve T cells and specific memory T cells, and might cause delayed-type hypersensitivity reactions.²⁴ The existence of HDM allergens coincident with epidermal DC in naturally occurring AD lesions has been reported in adult patients with IgE-allergic AD and HDM sensitization.²⁵ These findings suggest that not only IgE-dependent immediate hypersensitivity and IgE-mediated late phase reactions,^{26,27} but also IgE-associated delayed-type

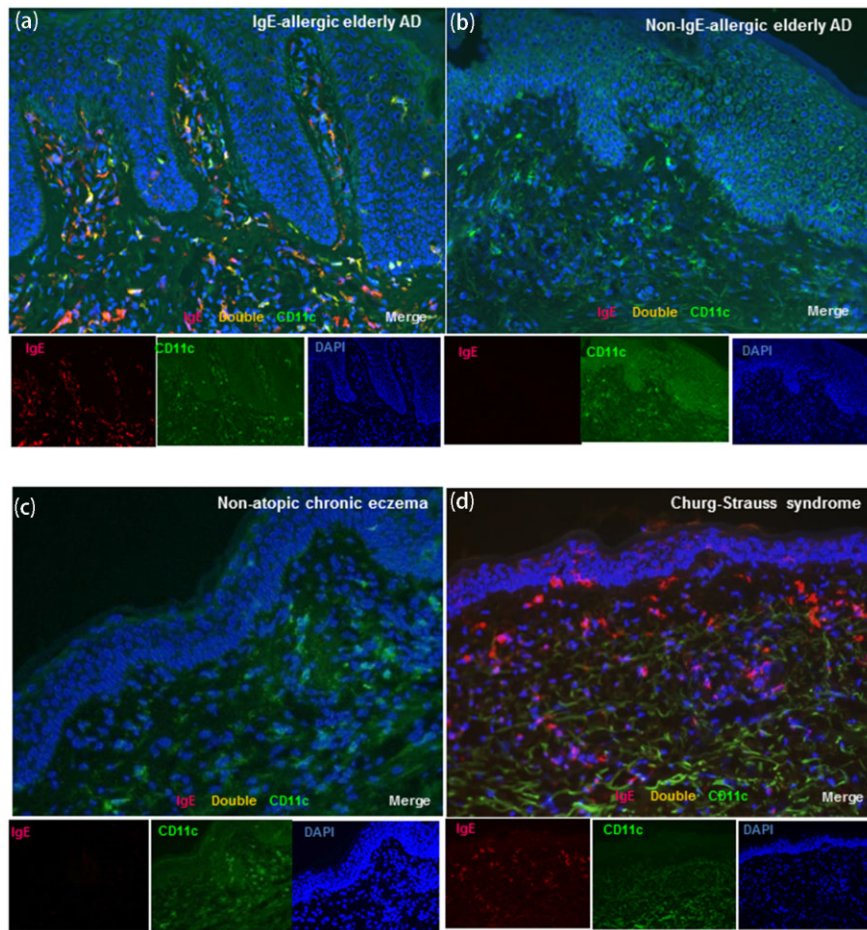


Figure 2 Double immunofluorescence staining with anti-immunoglobulin (IgE) and anti-CD11c monoclonal antibodies. (a) A lichenified skin lesion from a patient with IgE-allergic elderly atopic dermatitis. Double-positive IgE+ CD11c+ cells (yellow images) accompanied by single-positive IgE+ cells (red images) and single-positive CD11c+ cells (green images) are observed in the epidermis and upper dermis. The patient was a 71-year-old man with an elevated serum total IgE level of 2413 IU/mL and specific IgE for *Dermatophagoides farinae* and Japanese cedar.^{8,12} Figures reproduced with permission from the *Japanese Journal of Allergology*.¹² (b) A lichenified skin lesion from a patient with non-IgE allergic elderly atopic dermatitis. Only single CD11c+ cells (green images) are observed in the epidermis and upper dermis. The patient was a 63-year-old man with a serum total IgE level of 42 IU/mL and no detectable specific IgE for common environmental allergens. (c) An eczematous skin lesion from a patient with non-atopic chronic eczema (asteatotic dermatitis). Only single-positive CD11c+ cells (green images) are apparent in the epidermis and upper dermis. The patient was an 86-year-old man with a serum total IgE level of 16 IU/mL and no detectable specific IgE for common environmental allergens.⁸ (d) A skin lesion of vasculitis from a patient with Churg–Strauss syndrome. The majority of infiltrating stained cells in the upper dermis represent single IgE+ cells (red images). No double-positive IgE+CD11c+ cells (yellow images) are observed. The patient was a 78-year-old man with an elevated serum total IgE level of 3007 IU/mL and weak positivity for specific IgE for *D. farinae*.¹² Figures reproduced with permission from the *Japanese Journal of Allergology*.¹² Nuclei are labeled with 4',6-diamidino-2-phenylindole (DAPI, blue images). Original magnification: $\times 200$.

hypersensitivity reactions^{24,28,29} might contribute to the immune-pathomechanisms of skin lesions in IgE-allergic elderly AD.

In non-IgE-allergic AD (AD with normal levels of total IgE and a lack of sensitization to environmental allergens) and indeterminate-allergic AD (AD with normal levels of total IgE and positivity for allergen-specific IgEs or with high levels of total IgE and non-detectable allergen-specific IgEs),^{9,19} microbial components (e.g. *S. aureus* and resident fungi)^{7,30} and metal antigens¹⁸ might be the main triggers for allergic

skin inflammation in AD, in which Th1 responses (delayed-type hypersensitivity) and/or Th17/Th22 responses presumably evolve.^{2,31}

Onset and clinical course

Two types of clinical course and three patterns of AD onset were mainly seen for elderly AD: geriatric onset (continuous type); geriatric recurrence with a history of classic childhood AD (outgrow-recurrence type); and continuation and/or recurrence of adult AD (both

continuous and outgrow-recurrence types with a history of infantile-, childhood-, adolescent- or adult-onset AD). In our clinical study of 60 cases (IgE-allergic AD, $n = 38$; non-IgE-allergic AD, $n = 13$; indeterminate-allergic AD, $n = 9$),⁹ the frequencies of AD among elderly patients with IgE-allergic AD (AD with a total IgE level >400 IU/L and positivity for allergen-specific IgE) and non-IgE-allergic AD (AD with a total IgE level ≤ 400 IU/L and a lack of sensitization to environmental allergens) in geriatric-onset AD were 63.2% ($n = 24$) and 53.8% ($n = 7$), the frequencies of geriatric recurrence with a history of classic child AD were 7.9% ($n = 3$) and 7.7% ($n = 1$), and the frequencies of continued and/or recurrent adult AD were 28.9% ($n = 11$) and 38.5% ($n = 5$), respectively. In addition, 15.8% ($n = 6$) of elderly patients with IgE-allergic AD and 15.4% ($n = 2$) of those with non-IgE-allergic AD had a history of childhood AD. Meanwhile, instances of AD among elderly patients with indeterminate-allergic AD (AD with a total IgE level ≤ 400 IU/L and positivity for allergen-specific IgE or with a total IgE level >400 IU/L and non-detectable allergen-specific IgE) were concentrated in geriatric-onset AD (100%; $n = 9$).⁹ In a clinical study from Poland of 121 cases, the incidence of geriatric-onset AD, geriatric recurrence with a history of classic child AD, and adult-onset AD (another classification) were approximately 21%, 67% and 12%, respectively.⁷ We speculate that this discrepancy in the incidence of each type of elderly AD between Japan and Poland might be related to differences in the era of AD concept establishment, prevalence of infantile and childhood AD before the 1960s, and the medical record system in each country.

Complications

In terms of complications, some interesting findings were observed among the elderly patients with AD in our clinical study, in which the Mann–Whitney *U*-test or Kruskal–Wallis test was used for statistical analysis.⁹

AD-associated disorders

In IgE-allergic elderly AD ($n = 38$), elderly patients with the outgrow-recurrence type of early life-onset (until young adult phase) AD ($n = 5$) showed a higher incidence of childhood BA (60%; $n = 3$) than those (0%; $n = 0$) with the continuous type of early life-onset AD ($n = 8$). Elderly patients with the continuous type of early life-onset AD only showed an incidence of BA starting after the young adult phase (two patients had a history of BA-onset in the late-adult or senile phases). In addition, a personal history of childhood BA was also observed in elderly patients with geriatric-onset AD. These findings suggest that the so-called atopic march (allergic march) might extend to the senile phase in

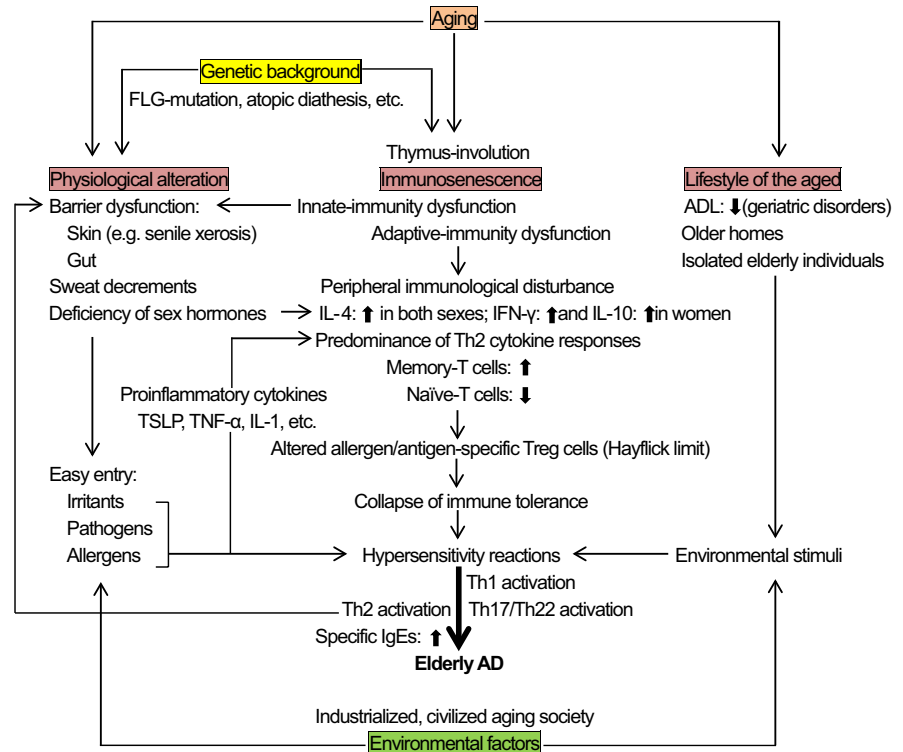
elderly patients with IgE-allergic AD.^{32,33} Meanwhile, in indeterminate-allergic AD and non-IgE-allergic AD, a personal history of childhood BA was not observed in elderly patients.⁹

A significantly lower incidence of ichthyosis was observed in elderly patients with IgE-allergic AD (2.6%, $n = 1$) as compared with patients with indeterminate-allergic AD (33.3%, $n = 3$; $P < 0.05$) or non-IgE-allergic AD (23.1%, $n = 3$; $P < 0.05$) in our study.⁹ This result is supported by a previous study for adolescent/adult AD that presented a tendency toward a lower incidence of ichthyosis in IgE-allergic AD compared with non-IgE-allergic AD.³⁴ Meanwhile, ichthyosis-related gene mutation of filaggrin (FLG) – a protein with a key role in epidermal barrier function – is now thought to be the most widely reproducible genetic risk for AD, and other forms of dermatitis and allergic disorders. Decreased expression of FLG has been observed both in AD lesional skin and non-lesional atopic skin.³⁵ Several recent investigations have suggested a strong association between FLG mutation and the development of AD in IgE-allergic AD patients (approximately 30% of the AD population) and the role in the development of atopic march in the childhood to adolescent phase.^{36–38} Analyses of FLG mutation in elderly patients with AD have not been widely carried out. We analyzed several FLG mutations (3321delA, Q1790X, Ser2554X, Ser2889X, Ser3296X and Lys4022X) associated with the Japanese AD population^{37,38} in two elderly patients with IgE-allergic AD (one with continuous-type adolescent-onset AD and another with continuous-type late adult-onset AD) who had participated in that clinical study and lacked complicated ichthyosis, but we could not detect any change to risk.¹² In view of these data, FLG mutation might not represent a crucial genetic risk for the development of IgE-allergic AD in older adults.

Malignancy

For elderly patients with AD, intriguing characteristics might be obtained from our retrospective analysis.⁹ The incidence of malignancy (5%; $n = 3$) in elderly patients with AD ($n = 60$; 41 men, 19 women; aged ≥ 60 years; mean age 77.1 ± 8.6 years; mean duration of follow up 51.3 ± 48.9 months) was significantly lower than that (31.9%, $n = 23$; $P < 0.05$) in control subjects (elderly patients with benign epidermal cyst; $n = 72$; 47 men, 25 women; aged ≥ 60 years; mean age 74.7 ± 7.0 years; mean duration of follow up 57.7 ± 46.7 months). For each clinical type, only the incidence of malignancy (2.6%; $n = 1$) in elderly patients with IgE-allergic AD ($n = 38$; 27 men, 11 women; aged ≥ 60 years old; mean age 76.2 ± 8.7 years, mean duration of follow up 51.0 ± 46.1 months [unpubl. data]) was significantly lower than that of the control subjects ($P < 0.05$).

Figure 3 A possible pathomechanism of elderly atopic dermatitis (AD). In addition to the genetic backgrounds and environmental factors, aging-related changes; that is, the immunosenescence, deficiency of sex hormones, barrier dysfunctions in the skin and gut, disturbance of sweat function, and environmental stimuli in the lifestyle of the aged, might play an important role in the pathogenesis of elderly AD. ADL, activities of daily living; FLG, filaggrin; IgE, immunoglobulin E; IL, interleukin; IFN- γ , interferon gamma; Th, T-helper; TNF- α , tumor necrosis factor alpha; Treg, T-regulatory; TSLP, thymic stromal lymphopoietin.



Furthermore, elderly patients with AD tended to show a lower incidence (0%; $n = 0$) of mortality from malignancy than control subjects (44.4%; $n = 4$), although the difference did not reach the level of significance because of the small number of cases (death was confirmed by our hospital in nine patients with elderly AD: IgE-allergic AD, $n = 6$; indeterminate-allergic AD, $n = 1$; and non-IgE-allergic AD, $n = 2$; and in nine of the control subjects). Although the limitations of retrospective analysis and a small sample size must be considered, these results suggest the hypothesis that the disease state in elderly AD, possibly mostly in a state of IgE-allergic AD, might involve immunological peculiarities acting against malignancy as a result of the over-response against foreign substances, including self-antigens, in which cancer antigens could participate.^{1,2}

Prognosis

The majority of elderly AD patients achieve amelioration of the skin manifestations once they receive suitable management in later life. Using standard treatments (e.g. moisturizers and topical corticosteroids for skin lesions on the entire body, topical tacrolimus for skin lesions on the face and neck, oral antihistamines, and oral anti-allergic drugs)¹¹ and combined therapy (standard treatments with oral corticosteroids), our clinical study ($n = 52$)⁹ achieved clinical improvement and clinical remission in 80.8% ($n = 42$) and 36.5% ($n = 19$; 19 of the 42), respectively, of cases with

elderly AD. The definition of clinical improvement and clinical remission⁹ were as follows: clinical improvement was defined as: (i) the disappearance of skin lesions in more than 95% of lesional areas observed within 5 months with only standard treatments; or (ii) the same disappearance observed for 6 months or more with combined therapy at a dosage of prednisolone at ≤ 5 mg/day after decreasing of oral corticosteroids; whereas clinical remission was defined as: (i) the same disappearance of skin lesions observed for 6 months or more with only standard treatments; or (ii) the same disappearance of skin lesions observed for 6 months or more even after withdrawal of oral corticosteroids in combined therapy. In our clinical study of elderly patients with moderate to severe AD, 27 patients received oral corticosteroids.⁹ The mean initial dosage of corticosteroids in combination with standard treatments was 7.7 ± 4.1 mg/day in prednisolone-equivalents, and 77.8% ($n = 21$) of the patients achieved clinical improvement; of these patients, 29.6% ($n = 8$) achieved clinical remission.

However, complete remission (outgrowth, a condition without any need for treatment) rarely arises in elderly AD. Most elderly AD patients will reach the end of life with AD.

Etiology of elderly AD

A possible pathomechanism of elderly AD is shown in the scheme (Fig. 3).

Pathophysiology

Immunosenescence

The adaptive (acquired or specific) immune system – in which T cells play a central role – is immature and does not function well in the early stages after birth. Activity develops in the childhood phase, peaks in puberty and declines gradually thereafter.³⁹ The clinical course of infantile and childhood AD can thus be speculated to be influenced by the maturation of the adaptive immune system. In elderly AD, aging of the immune system; that is, immunosenescence that involves thymic involution and subsequent age-related declines in T cell functions, might play an important role in the pathogenesis.¹¹ This hypothesis is supported by the observation that primary T cell immune-deficiency disorders frequently show AD-like eczema with high serum levels of IgE.¹⁷ In general, after 50 years-of-age, the entire T cell supply is generated virtually from existing naïve and memory T cells in the periphery, rather than from the involuted thymus.⁴⁰ Naïve T cells are reduced with aging, but memory T cells are concomitantly increased.^{39,40} Allergen-specific Treg cells that include IL-10-secreting Treg type-1 cells and other Treg subsets play a major role in peripheral immune tolerance to inhibit the development of allergic diseases and AD.^{41,42} In elderly individuals, the homeostasis of Treg cells is maintained by the expansion of existing naïve- and memory-like Treg cells, and possible conversion of non-regulatory T cells (e.g. Th17 cells) into Treg cells.⁴³ However, such renewal is probably restricted by telomere-length limitations (Hayflick limit), leading to alterations to the phenotypes and functions of Treg cells, which might then induce the collapse of immune tolerance and activation of hypersensitivity reactions to environmental allergens/antigens in elderly patients with a genetic diathesis.^{43,44} Conversely, immunosenescence has been shown to not affect total and specific IgE levels in elderly patients with IgE-allergic AD.⁴⁵ A tendency for the systemic Th1/Th2 balance to shift towards Th2 cytokine responses with aging might also be associated with the etiology of elderly AD.⁴⁶

Effects of sex hormones

Sex hormones appear to influence the immune system in humans. Pietschmann *et al.* showed that T cells from elderly women – but not from elderly men – were more frequently positive for interferon- γ and IL-10.⁴⁷ They also found that age-associated increases in the IL-4 production capacity of T cells seen in both sexes might be a result of androgen deficiency, and the selective increase to the interferon- γ production capacity of T cells seen in elderly women could be a consequence of estrogen deficiency. That study showed that average serum levels of testosterone in men and estradiol in

women were significantly lower in older adults than in younger adults, and interestingly, average serum levels of estradiol were clearly lower in older women than in older men.⁴⁷ These results might give some insights into why elderly AD, especially the IgE-allergic type, predominantly develops in men.⁹

Barrier dysfunction

Dysfunctions of the physiological, biochemical and immunological (chiefly innate immunity) barriers, not only in the skin, but also in the gut, might be involved in the pathogenesis of AD. Dry skin is common in infants and children as part of the normal skin physiology before puberty, although genetic predispositions, such as mutation of FLG and other candidate genes involved in skin barrier function, seem to influence disease severity. Barrier impairment under dry skin conditions might thus be thought to represent a major cause of infantile and childhood AD, and even for the start of atopic march in association with complicating allergic respiratory diseases. Barrier defects in dry skin facilitate the entry of irritants (e.g. sweat, inappropriate clothing), pathogens (e.g. *S. aureus*) and allergens (e.g. HDM, pollens, fungus and foods), and promote the expression of pro-inflammatory cytokines and chemokines; for example IL-1, tumor necrosis factor alpha and thymic stromal lymphopoietin, which increase Th2 responses and further decrease FLG generation.^{48–51} Meanwhile, the immature barrier function of the gastrointestinal tract could predispose atopic infants to IgE reactivity directly against various foods, particularly eggs, cows' milk, wheat and soy. However, most patients outgrow food allergies after 3 years-of-age as a result of the oral tolerance caused by maturation of the gastrointestinal barrier function and mucosal immunity.^{17,52} These findings suggest that natural resolution of classic childhood AD would occur with the development of barrier function in the skin and gut, in addition to maturation of the adaptive immune system during growth.

Declines in those barrier functions associated with aging might thus increase susceptibility to environmental irritants, pathogens and allergens that can lead to systemic sensitization, and/or induce a collapse in peripheral immune tolerance as elderly AD. In fact, decreased immunohistochemical expression of FLG has also been observed in age-related physiological dry skin (senile xerosis) of older adults,⁵³ and a possible role of senile xerosis in sensitization to environmental allergens in older adults has been suggested.⁵⁴ In addition, a recent clinical study showed that an increased risk of xerosis in older adults is associated with a history atopic disease, particularly AD.⁵⁵ Meanwhile, in relation to food allergy in older adults, it has been shown that IgE-mediated food allergy against celery, which is

frequently associated with birch-pollen allergy as a result of IgE cross-reactivity,⁵⁶ could be induced in accordance with decreased gastric proteolysis in elderly patients.⁵⁷

Sweat decrements

Sweat is one factor exacerbating AD.⁵⁸ However, recent studies have shown conflicting roles for sweat in the pathogenesis of AD. Both an antimicrobial peptide, dermcidin and a proteinase inhibitor, cystatin A, contribute to innate immunity and barrier function at the skin surface, and are functionally produced by sweat glands.^{50,59} Cystatin A inhibits exogenous cysteine proteases from HDM (e.g. *D. farinae* 1, *D. pteronyssinus* 1) that could break down the epidermal barrier.^{50,60} Immediate hypersensitivity against sweat was observed in approximately 80% of patients with AD,⁶¹ and a sweat antigen, MGL-1304, is secreted by a resident fungus, *Malassezia globosa*.⁶² Most AD patients show a defective ability to deliver sweat to the skin surface as a result of dysfunctional closure of the sweat gland orifices, which might induce entry of sweat into the dermal tissues adjacent to the sweat glands and cause inflammation in sensitized patients.⁵⁹ Such findings might also be associated with the pathogenesis of elderly AD. In contrast, regional sweating in older adults decreases with age.⁶³ Age-related regional sweat decrements might thus be speculated to be related to the pathophysiology and features of skin manifestations in elderly AD, such as the reverse sign of lichenified eczema around the folds of the elbows and knees.⁶⁴

Life environment of older adults

In elderly patients with AD, environmental stimuli caused by common geriatric problems and lifestyle changes; for example, decreases in activities of daily living, lower ability of self-care and isolated elderly individuals, might be associated with a development and aggravation of the disease state. Indeed, a positive relationship between a lower level of activities of daily living and higher probability of asteatosis (dry skin condition) has been reported among elderly residents in care institutions.⁶⁵ In addition, elderly individuals generally live in older homes, which have been suggested to contain higher levels of HDM allergen (*D. pteronyssinus* 1), with an increased risk of sensitization to the HDM allergen.⁶⁶

Diagnosis and management of elderly AD

Diagnosis of elderly AD

The diagnosis of elderly AD is difficult, because elderly individuals often have pruritic skin disorders; for

example, asteatotic dermatitis, senile pruritus and chronic prurigo, and commonly have other coexisting/underlying disorders; for example, hypertension, cardiac/cerebral vascular diseases, gastrointestinal disorders and diabetes mellitus, which possibly induce itchy conditions caused directly by the medical conditions and/or as side-effects of medications. This might complicate the diagnosis of elderly AD. Even now, definitive clinical, histopathological and laboratory diagnostic markers are lacking.⁶⁷ Therefore, for the diagnosis of elderly AD, a long follow up (more than 6 months) of the clinical course of the skin manifestations and analysis of the diagnostic features of AD using standardized criteria are required.¹¹ Diagnosis by exclusion from other pruritic skin conditions under laboratory examinations and/or allergic skin tests is also required for elderly AD, especially for non-IgE-allergic elderly AD.⁶⁸ Furthermore, histopathological analyses are often required to exclude other severe diseases, such as adverse drug reactions, idiopathic/secondary erythroderma^{69,70} and cutaneous T cell lymphoma.⁷¹

Management

In general, management of AD is carried out in accordance with the standardized guidelines of practice for AD.^{72–74} Management comprises treatment to protect the skin barrier (e.g. moisturizers and emollients), anti-inflammatory measurements (e.g. topical corticosteroids, topical calcineurin inhibitors, such as tacrolimus and oral antihistamines), and the identification and avoidance of trigger factors (e.g. environmental allergens). Management of elderly AD should basically conform to this concept.¹¹ In addition, oral administration of anti-allergic drugs, such as suplatast tosilate (a Th2 cytokine inhibitor), disodium cromoglycate (an anti-allergic agent for food sensitization and/or metal allergy) and montelukast/pranlukast (leukotriene antagonists), would be effective in patients with raised serum levels of IgE, and/or thymus and activation-related chemokine (a biomarker of Th2 cytokine responses), positive results for specific IgE to food allergens or metal patch tests, and complications of BA and/or AR.⁷⁵ Regular application of moisturizers and emollients in combination with topical corticosteroids and tacrolimus, and oral antihistamines and anti-allergic drugs have been the standard treatments for the disease.

In older patients, avoiding trigger factors in the environment and applying sufficient topical medication is difficult, because of the decreased activities of daily living with aging and lifestyle (e.g. isolated elderly individuals). Therefore, for moderate to severe cases, oral corticosteroid therapy can be used with the aforementioned standard treatments. However, this requires appropriate monitoring and prevention of

adverse events, such as hypertension, peptic ulcer, cataract, osteoporosis, diabetes mellitus and steroid purpura.

As other adjunctive treatments, oral cyclosporine is very effective for the treatment of severe cases of elderly AD, but clinicians must pay attention to the increased risk of malignancy and organ toxicity (e.g. renal dysfunction) in older adults.⁷⁶ Narrowband ultraviolet B at a dose of approximately 0.35–0.65 J/cm² per irradiation appears extremely effective for elderly AD.^{77,78} Therapeutic patient education⁷⁹ and a psychodermatological approach⁸⁰ are also useful for avoiding trigger factors and modifying problematic behaviors, such as habitual scratching.

In recent years, new groups of therapeutics; for example, anti-pruritic drugs,⁸¹ allergen-specific immunotherapy⁸² and biologics,⁸³ have been used in patients with moderate to severe AD as pilot studies or double-blinded controlled trials. However, representative, randomized, placebo-controlled studies evaluating the efficacy and safety of these therapeutics for AD have yet to be completed.^{2,73}

Future directions

In the near future, AD will become an ordinary disease of elderly individuals in an aging society. The natural lifetime courses of AD in accordance with the genetic background, environmental stimuli and heterogeneous clinical phenotypes will become apparent. Risks for the development of elderly AD in patients with or without a history of infantile-, childhood-, adolescent- and adult-onset AD will also eventually become apparent. Genetic and biological research will inevitably bring further insights into the pathophysiology of AD and advances in the diagnosis of AD. Research might also result in preventive and/or personalized therapies for AD in the future based on clinical phenotyping and molecular taxonomy,^{2,84,85} not only in patients with classic child and adult AD, but also in patients with elderly AD. Further investigation of a large cohort of elderly patients with AD is warranted.

Conclusion

AD in older adults represents a new subgroup of AD. The characteristics of elderly AD might be attributed to specific features of gerontology in older adults; that is, immunosenescence, changes in the sex hormone milieu, age-related barrier dysfunctions in the skin and gut, disturbance of sweat function, and environmental stimuli in the elderly lifestyle. Most elderly patients with AD reach the end of life with AD, which should now be considered a lifelong allergy disease.

Acknowledgments

The authors express their thanks to Professor Motoji Sawabe (Department of Molecular Pathology, Tokyo Medical and Dental University), Professor Emiko Noguchi (Department of Medical Genetics, Tsukuba University) and Honorary Professor Kensei Katsuoka (Department of Dermatology, Kitasato University School of Medicine) for their kind cooperation.

Disclosure statement

The authors declare no conflict of interest.

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