Atopic dermatitis in the elderly

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Abstract

Atopic dermatitis (AD) is a recurrent skin inflammation accompanied by itching. The incidence of AD is increasing worldwide. AD, which persists until elderly or with an onset during elderly, is known as senile AD. It has different prevalence and clinical features from other AD stages. Senile atopic dermatitis affects males more than females, which is different from other stages of AD. Skin manifestation of senile AD is similar with the adult stage of Hanifin-Rajka criteria, but can be atypical. The typical feature of senile AD is eczematous dermatitis around a free-lesion fossa. Other common clinical manifestations are erythroderma and non-specific chronic dermatitis. In the management of senile AD, changes related to aging process should be considered. Management of senile AD is complex, involves combined pharmacological treatment consists of topical and systemic agents, and non pharmacological aspects. Appropriate treatment considering effectiveness and safety will improve the quality of life of patients with senile AD.

Keywords: atopic dermatitis, elderly, clinical feature, senilis, atypical

Introduction

Atopic dermatitis (AD) is a chronic recurrent skin inflammation, which is accompanied by itching and occurs in certain predilection site. The disease is commonly found in infants, children and adults. The incidence of persistent AD or those with adult onset is increasing in many developing countries. Atopic dermatitis affects 1-3% adult and elderly patients.
According to the definition by the World Health Organization (WHO), elderly are those aged over 60 years. The population of elderly increased almost three folds between 2012 and 2013. The aging process causes various reduced skin function, which leads to atypical clinical features of AD in elderly.

**Epidemiology**

AD affects 20% children of industrial countries worldwide, but lower prevalence is found in agricultural countries. The International Study of Asthma and Allergies in Childhood (ISAAC) demonstrates that the incidence of AD is increasing, particularly in developed and developing countries and women are more affected than men. In 2012, there were 1.1% AD patients aged 13-14 years in Indonesia. Reports from five hospitals that provide pediatric dermatology care in Indonesia show that there are 261 AD cases among 2,356 new patients (11.8%).

Data on the prevalence of senile AD is limited since it is an uncommon subtype. It has been reported that the prevalence is 0.6% per year in Mexico and 2.6% per year in Japan. A study in German has reported that the prevalence range of senile AD is 1.5-10% in those aged over 50 years; while in Iran, it is only 1.5%. It has also been reported that atopic dermatitis is found in 0.5% of elderly patients who have skin complaints in India. Unlike the children and adult stage AD, senile AD affects men more than women with a ratio of 3:1. The data is established based on results of nine years studies in Japan and Australia.

Based on the data from the Geriatric Division of Outpatient Clinic in Department of Dermatology and Venereology, dr. Cipto Mangunkusumo National Hospital, there were 57 patients out of the total visit of AD patients between January 2013 and August 2014. The number of new senile AD patients of the total visit was 13 patients with greater prevalence in women as compared to men (8:5).

**Pathogenesis**

**Etiology**

AD is categorized into two types, i.e. the extrinsic/allergic type and intrinsic/ non-allergic type. The extrinsic type is found in 70-80% of AD patients. In this type, there is sensitization to environmental allergen and increased serum IgE; while the intrinsic type is found in 20-30% of AD patients. In intrinsic type, there is no sensitization to environmental allergen and the serum level of IgE is low.

Tanei reports that the frequency of senile AD with pure intrinsic type is 6.25%; while the mixed type (with a history of asthma) is 12.5%. Katsarou and Armenaka demonstrate that the prevalence of extrinsic AD is higher than the intrinsic type. Results of a study conducted by Folster-Holst, et al. shows that extrinsic type of senile AD is more common than the intrinsic type and it is usually found in patients with a family history of atopy.

In general, the pathogenesis of AD is a complex interaction of genetic susceptibility, the host environment, epithelial barrier dysfunction and dysregulated immune response. This concept is also applicable to senile AD.

**Genetic susceptibility**

A study has reported that there are some gene mutations in AD patients, i.e. coding genes of T helper (Th)2 cytokines including interleukin (IL)-4 and IL-13 genes on chromosome 5q31-33, serine protease inhibitor Kazal type 5 (SPINK5) gene on chromosome 5q31, IL-4 receptor gene on chromosome 16p12.1-11.2, mast cell chymase gene on chromosome 14q11.2 and filaggrin gene on chromosome 1q21.

The gene mutation of filaggrin is the most commonly found mutation in AD patient. The gene mutation will reduce its role in retaining water (transepidermal water loss/TEWL) and maintaining skin flexibility. Decreased expression of filaggrin can be observed in the skin lesion and also unaffected skin of patients with AD. A study in Europe demonstrates that a mutation on chromosome 1q21 is a predisposing factor for persistent early onset atopic dermatitis and extrinsic type in adults; however its effect on other atopy manifestation is not known. Unfortunately, until now, there has been no report on a study analyzing the gene mutation, particularly in senile AD population.

**The host environment**

Exposures to allergens, irritants and environmental pathogens are associated with AD incidence. House dust mite of Dermatophagoides genus is found at ten folds concentration in the homes of AD patients. Patients with senile AD, especially those aged 75 years and over, experience reduced daily living activities that increases the risk of exposures to allergens (house mite, pollen, molds, food), irritants.
Epithelial barrier dysfunction
Defects in epithelial barrier in AD patients occur in the skin and gastrointestinal tract. It explains the development of IgE reactivity in atopic children against various foods that takes place in approximately 40% of patients with childhood AD. The epithelial function of gastrointestinal tract improves with the increasing age; therefore, most patients will be tolerant against food allergies by the age of three. Aging will cause recurrent dysfunction of the gastrointestinal epithelial barrier and subsequently increases the susceptibility of elderly patients to food allergens. The process of allergen, irritant and pathogens introductions can lead to systemic sensitization in elderly patients with AD.1,5

Mutation of filagrin gene causes reduced natural moisturizing (NMF) level resulting dry skin. It is worsened by reduction of water content and lipid level in the stratum corneum, changes in ceramide structure and inefficient degradation of corneodesmosome in the elderly skin.19-21 Combination of those various problems will cause skin xerosis of the elderly which become the port d'entrée of various allergens, irritants and pathogens.5,19-21

Dysregulated immunologic response
In AD patients, there is predominant systemic Th2 cells level followed by abnormal IgE production, peripheral eosinophilia, activation of mast cell and cytokine induction (e.g. IL-4 and IL-13). Analysis on extrinsic and intrinsic type shows increased Th2 cells and reduced Th1 cells in AD patients. The acute phase of AD will have Th2 cell predominance, while the chronic phase of AD will be affected by the production of Th1 cells cytokines, i.e. IL-12, IL-18, IL-11 and transforming growth factor (TGF)-β1.1, 5, 22 Recently, IL-31 cytokines production has been reported as one of the causes of itching in AD.23 Eosinophilia is one of the important markers for AD. There is an increase of CD69 and CD 38 expressions as markers of the activation, which can be detected in peripheral blood. The possibility that these findings may affect the severity of disease is still vague.24

The aging of the immune system that involves thymic involution has important role in the pathogenesis of senile AD.22 The overall number of T cells is significantly decreased in those aged over 75 years. Naive T cells are reduced, particularly the CD8, but memory T cells are increased.25,26 The hypothesis is supported by the incidence of AD-like dermatitis found in primary T cell immunodeficiency disorders.5,22 The aging process also relatively reduces the level of suppressor T cells, which may induce an activation of hypersensitivity reactions and intolerance to environmental allergens in elderly patients.26,27 Table (1) shows details of altered immune response experienced by elderly patients.28

Inducing factors
1. Allergen and irritant
Sensitization occurs in senile DA, particularly in moderate to severe condition, except for food sensitization, which has lesser roles in senile DA. Food may have its role through the non-allergenic pathway such as alcohol and food preservatives that induce exacerbation through the non-immunological mechanism. Results of prick test against food are not always positive for adult AD patients who show a response to food. 5

The levels of total IgE and specific-aero allergen are increased in AD patients of all stages and they tend to be stable with increasing age. A study has reported that 86% of senile AD patients have IgE-specific-aero-allergen, particularly to house dust mite and pollens.5,17 Tanei et al have found that there is IgE-mediated inflammation in senile AD, particularly the extrinsic type. Researchers have also reported that the total IgE level in patients with a history of adult onset is higher compared to patients with childhood onset.29

The correlation between atopy and allergen contact is still unclear. However, atopic dermatitis is a risk factor for sensitization of allergic contact dermatitis.30 A study involving adult AD patients in Scandinavia found that the results of patch test had positive relevance for at least one allergen, particularly on nickel.5 Atopic dermatitis can be exacerbated by irritants. Excessive washing, soaps and detergents will induce flare of AD.4,31 Atopic dermatitis is also the most common cause of occupational dermatitis, and it increases the risk of irritant contact dermatitis by two folds, particularly for those occupations involving wet work.5,31
## Table 1. Summary of Immunosenescence features

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Changes with aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Reduced phagocytosis</td>
</tr>
<tr>
<td></td>
<td>Reduced reactive oxygen species production</td>
</tr>
<tr>
<td></td>
<td>Defect in apoptotic cell death</td>
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<tr>
<td>Eosinophils</td>
<td>Reduced degranulation</td>
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<tr>
<td></td>
<td>Reduced superoxide production</td>
</tr>
<tr>
<td>Monocytes/macrophages</td>
<td>Reduced phagocytosis</td>
</tr>
<tr>
<td></td>
<td>Reduced cytokine and chemokine secretion</td>
</tr>
<tr>
<td></td>
<td>Reduced generation of nitric oxide and superoxide</td>
</tr>
<tr>
<td>Mast cells</td>
<td>Reduced degranulation</td>
</tr>
<tr>
<td></td>
<td>Dysregulation in function</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Reduced phagocytosis and pinocytosis</td>
</tr>
<tr>
<td></td>
<td>Increased IL-6 and TNF-alfa production</td>
</tr>
<tr>
<td></td>
<td>Diminished TLR expression and function</td>
</tr>
<tr>
<td></td>
<td>Dysregulation in function</td>
</tr>
<tr>
<td>T cells</td>
<td>Reduced response and proliferation</td>
</tr>
<tr>
<td></td>
<td>Reduced TCR diversity</td>
</tr>
<tr>
<td></td>
<td>Reduced signal transduction</td>
</tr>
<tr>
<td></td>
<td>Dysregulation in function</td>
</tr>
<tr>
<td>B cells</td>
<td>Production of low-affinity antibodies</td>
</tr>
<tr>
<td></td>
<td>Increased oligoclonal expansion</td>
</tr>
<tr>
<td></td>
<td>Decline in serum total IgE values</td>
</tr>
<tr>
<td></td>
<td>Reduced surface MHC class II molecule expression</td>
</tr>
<tr>
<td></td>
<td>Dysregulation in function</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>Impaired production of cytokines</td>
</tr>
<tr>
<td>NK cells and NKT cells</td>
<td>Decreased clearance of particles</td>
</tr>
</tbody>
</table>

*Data obtained from reference no. 28

2. **Microorganism**

Skin infection, colonization of skin microorganisms and sensitization to skin microorganisms are predisposing factors of AD. Microorganism can be an inducing factor for eczematous reaction in sensitized AD patients. Colonization of *Staphylococcus aureus* has been reported to be relatively high in adult AD patients (86%) and the IgE level, which is specific to toxins, is associated with the severity of dermatitis. The highest prevalence of IgE (92%) against enterotoxin has been seen in adult patients with total IgE level of >2000 IU/mL. *S. aureus* toxins increase immune response and causes chronic dermatitis in 34% of adult patients.\(^2,4,5\)

Colonization of *Malassezia* is more commonly found in AD patients with adulthood stage than those with childhood stage, which is supported by findings of specific IgE level against Malassezia species in most of adult AD patients with increased total IgE level. Specific sensitization to *Malassezia sympodialis* has been found in many AD patients with extrinsic type (50-64%) and intrinsic type (36-50%). Patients with chronic dermatitis are susceptible to sensitization.\(^5\)

3. **Psychological stress**

There is a complex psycho-neuro-immunological involvement in AD patients. Stress changes the function of skin barrier, T cells and antimicrobial immune response. Stress also induces itching, which will be followed by further skin damage due to scratching. AD is known to have a stress-related exacerbation. Stress is one of the important factors that can induce AD. Intervention to reduce psychological stress can improve skin condition and patients’ quality of life.\(^1,5,32\)
Clinical manifestations

The major and typical subjective complaint of AD is itching, that can be so severe that it causes sleep disturbance. The efflorescence of AD lesion depends on the disease onset and severity. Acute lesion is characterized by circumscribed erythematous lesion, papule, papulovesicles, erosions and exudations. The subacute lesion appears as erythematous plaque, squamous lesion, excoriations and papules; while the chronic lesion consists of thick plaque, lichenification, hyperpigmentation or fibrotic papules (prurigo).³

The onset of senile AD consists of three forms, such as senile onset, recurrent with a history of classic AD in childhood, and recurrent and or continuity of AD in adulthood.¹,⁵⁻⁷

Skin manifestations of senile AD are identical with the adulthood stage when the diagnosis is established based on Hanifin-Rajka criteria. Signs of chronic dermatitis can be found on the face and neck including lichenification or exudative lesions on the trunk, lichenification with or without pruriginous papules and nodes on the extremities.⁵

The senile AD manifestation that can differentiate between the senile and adulthood stages is the involvement of elbows and knees. Local lichenification of both areas is uncommon in the senile stage unlike the adulthood stage AD. The noticeable feature of the senile stage is eczematous dermatitis around free-lesion fossa area. The feature is typical for senile stage, but not for other stages. Another typical feature that has been reported is erythroderma and non-specific chronic dermatitis.¹,⁵⁻⁷

The atopic stigma other than the above mentioned can still be found in senile AD such as the Hertoghe’s sign, erythematous and pale face, the dirty neck sign and papule with accentuation.¹

Management

The management of AD in Indonesia consists of 5 pillars; these are: ³
1. Providing educational and efficient endeavors for patients and their caregivers
2. Avoiding and modifying the environmental trigger factors and modifying lifestyle
3. Strengthening and maintaining the optimal function of skin barrier
4. Eliminating skin inflammation
5. Controlling and eliminating the scratch-itch cycle.

Further discussion on the management of AD is categorized into pharmacological (medicamentosa) and non-pharmacological (non-medicamentosa) treatment.

Pharmacological
1. Topical treatment

Topical treatment for senile AD consists of moisturizer, steroid, antibiotics, antiseptic and antifungal. Moisturizer is used on all skin surface, either affected or unaffected skin. The use of moisturizer is continued although the lesion has been healed. Ideal moisturizer should be able to provide well hydration to stratum corneum and can reduce TEWL. Skin barrier in elderly is impaired and hardly corrected; therefore, the ideal moisturizer should be emphasized more on improving appearances, keeping the skin comfortable and preventing further impacts of skin aging. The selection of moisturizer in senile AD patients is different for each individual. In general, moisturizer with emollient-dominant effect will give more advantage for senile skin. Additional of active ingredients, the hypoallergenic nature, the convenience and practical usage as well as the cost are factors to be considered in choosing the ideal moisturizer for patients.³³⁻³⁵

It is recommended to use topical steroid for acute lesion together with topical calcineurin inhibitor in order to prevent long term side effects of steroid treatment. Tacrolimus is more effective than pimecrolimus for adult patients with moderate to severe AD. The adult AD patients can tolerate the use of tacrolimus for 2-4 years.³⁶

The use of topical antibiotics, antiseptics, antifungal can be considered in order to reduce the number of bacterial and fungal colonization; however, care should be taken on the possibility of developing antibiotics resistance S. aureus.⁵,³⁶

2. Systemic treatment

In senile AD patients, it may be difficult for them to avoid trigger factors and to apply topical medication optimally as they have reduced daily activity; therefore, systemic treatment can be considered.

For acute lesion, short-term oral steroid treatment (prednisolone 20-40 mg) can be used.⁵ For elderly patients, the use should be monitored, particularly for the possibility of increased blood glucose, blood pressure, myopathy, osteoporosis, obesity, thrombosis, cataract and gastric ulcer. ³⁷

A sedative antihistamine (AH) can be used to reduce itching; however, precautions must be
taken on effectiveness and safety for the use in the elderly. The first generation of sedative antihistamine such as hydroxyzine, clemastine and dimethindene can reduce cognitive function and is considered as inadequate treatment. The second generation of AH, e.g. cetirizine, desloratadine, loratadine can be the appropriate choice to reduce itching. Administration of second generation AH need to consider patient safety principle, particularly patient’s kidney function.37

The antibiotic administration can be considered when there is a serious infection. The choices of systemic antibiotics are erythromycin, clarithromycin or cephalosporin for 7-10 days. Ketoconazole, which is specific for skin yeast is recommended for patients with IgE hypersensitivity; however, the recommendation of ketoconazole administration still need to be supported by larger studies.5 The administration of antibiotics and antifungal should consider patient’s kidney function and the possibility of interaction of concomitant drug treatment.37

The first line treatment for AD patients includes the above mentioned systemic and topical agents. The second line treatment, which is considered effective for senile AD is phototherapy, particularly the combination of ultraviolet (UV) UV-A and UV-B. In addition, for severe AD, cyclosporine may effectively reduce symptoms; however, the tolerance is lower and there is a higher possibility of nephrotoxicity and neurotoxicity in the elderly while compared to younger patients.36-37

It has been reported that the use of immunotherapy on Dermatophagoides provides improved AD. Subcutaneous injection using mite allergen extract can reduce basophil activation. The use of such immunotherapy in the elderly is not completely established either for its effectiveness or safety.38

A study has been conducted on dupilumab, a monoclonal antibody used in adult AD patients. The study reported that the administration of dupilumab reduces inflammation, itching, the incidence of infection and it is well tolerated by the patients.39

Many studies have been started on the role of vitamin D in AD patients. Vitamin D deficiency in senile AD patients occurs due to the AD disease and aging process itself. Elderly patients have reduced vitamin D synthesis three folds compared to adult patients. It is a common finding in some studies that supplementation of 4000 IU vitamin D daily for 21 days in AD patients can improve the Score of Atopic Dermatitis (SCORAD) significantly.40-41

Non-pharmacological
The primary principle of AD treatment is avoiding trigger factors. Food plays little role as a trigger in senile AD patients.33,36 Non-immunological process caused by alcohol and food preservative can be managed by pseudoallergen diet. It has been reported that 6-week pseudoallergen diet has provided clinical improvement for 60% of adult AD patients.5

A meta-analysis study has reported the use of probiotics as a treatment for moderate to severe AD patients, both in adults and children. The administration of probiotics with Lactobacillus species is effective in improving SCORAD of AD patients aged over one year.42

Atopic dermatitis can increase psychological stress and reduce patient’s quality of life significantly. Psychological stress can also affect the spouse of senile AD patients. Psychological intervention can help healing and can prevent recurrent AD in elderly patients.32

Conclusion
Atopic dermatitis in elderly or senile AD is still rarely reported. Almost all reports have showed that the prevalence of senile AD is higher in men than women. The most common clinical features are dermatitis around the folds of elbows and behind knees, erythroderma and non-specific chronic dermatitis. Aeroallergen has a greater role than food or contact allergen in senile AD. The management of the disease is complex since there are many physiological changes due to aging; therefore, treatment must be provided while considering effectiveness and safety. The quality of life of AD patients is a very important aspect; thus, care on the aspect should be taken in providing AD treatment for the elderly.

References
3. Diana IA, Boediardja SA, Soegito TL, Lokanata MD, Prihianti S, Danarti R, et al. Diagnosis and