

Adult Atopic Dermatitis in Hospitalized Patients: Comparison between Those with Childhood-Onset and Late-Onset Disease

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Keywords

Atopic dermatitis · Atopy · Childhood onset · Late onset

Abstract

Atopic eczema is one of the most prevalent diseases worldwide. It is a common dermatological disorder that affects 17.8 million individuals in the USA, up to 20% of children and up to 3% of adults. Recent data show that the incidence of the disease is still rising, both in children and adults, especially in low-income countries. Atopic dermatitis in adults consists of childhood-onset (COAD) and adult or late-onset types (LOAD). Prior research has described differences in clinical features, laboratory data, and response to treatment between COAD and LOAD. Most studies have been done on an ambulatory population that mostly contains patients with mild to moderate disease. **Objective:** The aim of the study was to describe the differences between adults hospitalized with COAD and LOAD. **Methods:** Data were analyzed from a retrospective cohort of 107 adult AD patients who were hospitalized from 2009 to 2017. Analysis of data included epidemiology, clinical and laboratory characteristics, and response to treatment. **Results:** Of the total sample, 87 (81%)

patients were diagnosed with LOAD, and 20 (19%) patients were diagnosed with COAD. The median age was 66 years for all patients, 42 years for COAD patients, and 77 years for LOAD patients. The prevalence of atopy was lower in the LOAD group than in the COAD group (33.8 vs. 68.8% for family history, 35.5 vs. 84.8% for personal history). A higher incidence of head, neck, and flexural involvement was found in COAD patients. LOAD patients had lower immunoglobulin E levels and responded better to phototherapy. **Conclusions:** Elderly patients with LOAD constitute the majority of adults hospitalized with AD. As in ambulatory AD patients, there are significant differences in medical background, clinical picture, laboratory characteristics, and response to treatment between hospitalized LOAD and COAD patients. There is a need to determine diagnostic criteria and treatment guidelines for these patients.

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Introduction

Atopic dermatitis (AD) is a chronic, inflammatory, and relapsing skin disease that mostly affects infants and children; this typical presentation is known as childhood-onset AD (COAD) [1]. While in most cases the disease subsides with age, occasionally it may persist into adulthood (persistent AD) or follow a chronic course of remissions and relapses (chronic-relapsing AD). It is a matter of controversy in the literature, however, whether AD may first develop among adults and elderly patients (known as adult-onset or late-onset AD – LOAD) or whether these cases represent pre-existing but unrecognized occurrences of the disease that express clinically only after many years.

Atopic eczema is one of the most prevalent diseases worldwide. It is a common dermatological disorder that affects 17.8 million individuals in the USA. Recent data showed that while AD seems to have reached a plateau in the countries with the highest prevalence such as the UK and New Zealand, AD continues to increase in prevalence, specifically in young children (age 6–7 as compared to age 13–14 years) and in low-income countries, such as Latin America or Southeast Asia [2].

The incidence of AD is about 15–30% in children and only 0.3–14.3% in adults [3]. While 60% of cases occur in the first year of life, 60–74% of cases are resolved before the age of 16, and the rest persist into adulthood [1, 4].

The term LOAD was coined by Bannister and Freeman [5] in 2000 when they observed that 10% of the AD cases seen in a hospital setting were adults. Other studies have shown that LOAD cases represent 9–24.5% of all AD cases, and their incidence varies from 1 to 3% in various populations around the world [4]. A recent review and meta-analysis have found that approximately 1 out of 4 adults with AD reports adult onset of the disease [6].

The diagnosis of AD among infants, children, and adolescents is usually based on clinical findings along with the personal and family history of atopy. While several diagnostic approaches have been established for the diagnosis of AD, the diagnostic criteria proposed by Hanifin and Rajka are the most commonly accepted [7]. Indeed, these criteria were developed specifically for children and have not been adjusted for adults [2]. Currently, LOAD has not been adequately studied and lacks standard and accepted criteria for diagnosis. This form of the disease is characterized by a high degree of heterogeneity. Moreover, the differential diagnosis of a new-onset pruritic eruption with eczematous features in an adult or an elderly person is broad, and papulosquamous diseases, contact dermatitis,

Table 1. Demographic characteristics and atopic comorbidities

Total (<i>n</i> = 107)	COAD, <i>n</i> (%)	LOAD, <i>n</i> (%)	<i>p</i> value
Number of participants	20	87	
Males	11 (55)	50 (57.5)	ns
Females	9 (45)	37 (42.5)	ns
Median age at diagnosis, years	42	77	<0.05
Ethnic origin			
Ashkenazi Jews	7 (50)	32 (49.2)	ns
Sephardic Jews	6 (42.9)	31 (47.7)	ns
Other	1 (7.1)	2 (3.1)	ns
Fitzpatrick skin type			
1, 2	7 (43.8)	20 (50)	ns
3	7 (43.8)	15 (26.8)	ns
4, 5	2 (12.5)	11 (19.6)	ns
Family history of atopy	11 (68.8)	24 (33.8)	0.01
Personal history of atopy	16 (84.2)	27 (35.5)	<0.001
Asthma	7 (35)	15 (17.2)	ns
Rhinitis	3 (15)	7 (8)	ns
Conjunctivitis	0 (0)	2 (2.3)	ns
Allergies to medications	13 (65)	30 (34.5)	ns
Positive patch test	4 (66.7)	17 (73.9)	ns

COAD, childhood onset atopic dermatitis; LOAD, late-onset atopic dermatitis; ns, no significance. Data are presented in numbers (%).

drug eruptions, infectious diseases, autoimmune diseases, bullous disease, or cutaneous lymphoma should be considered and excluded before establishing the diagnosis of LOAD. Most dermatologists make a diagnosis of LOAD based on clinical findings characterized by pruritic eczematous eruption with typical distribution, the presence of associated laboratory findings, and the exclusion of other AD-mimicking conditions.

The course of LOAD is different between patients and is characterized by intermittent exacerbations and improvements. Clinical characteristics vary depending on the age of the patient and whether the disease is in acute flare or in the chronic phase. In an article published by Liu et al. [8], a set of diagnostic criteria for LOAD has been proposed by Chinese researchers and includes three characteristics: symmetric eczema over 6 months (obligatory for diagnosis); personal/family history of atopy; and elevated immunoglobulin E (IgE) levels, including presence of IgE specific to allergens or eosinophilia. Pruritus is not a part of the criteria, as it was not found to be specific to this diagnostic entity [8].

Given the already described complexities in diagnosis of AD in adults in general and of LOAD specifically, as

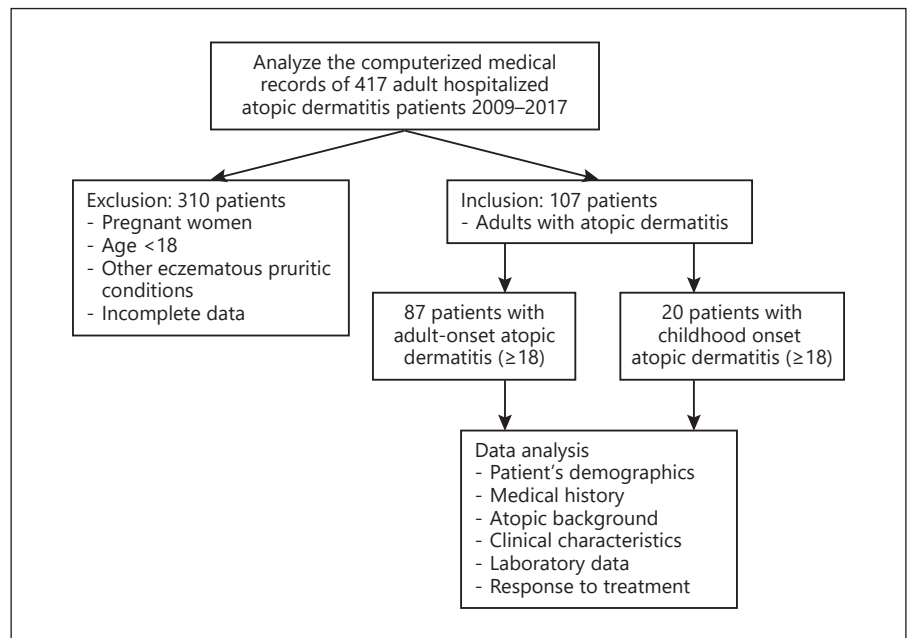


Fig. 1. Flowchart of the Patients and Methods.

well as the rise in the incidence of the disease in the developed world over the last 30 years [3], there is a need for separate diagnostic criteria for COAD and LOAD. This will allow a better diagnosis and management of adult patients with AD. Most studies on AD have been done on ambulatory patients. This population differs from hospitalized populations, which typically encompass only moderate to severe cases.

In the present study, we analyzed and compared various epidemiological, clinical, and laboratory characteristics, and the response to phototherapy of adults with COAD and those with LOAD.

Patients and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000499708 for all online suppl. material) (Fig. 1).

Results

Between 2009 and 2017, 417 patients were admitted to the dermatology department at the Sheba Medical Center with a diagnosis of AD. Of these, 310 were excluded from the study due to incomplete data, change of diagnosis, or uncertainty in the diagnosis.

Age and Gender

Thus, the study group included 107 patients, of whom 87 (81%) were diagnosed with LOAD, while 20 (19%) were diagnosed with COAD. The patients' demographic characteristics are shown in Table 1. The median age across participants in all groups was 66 years (IQR 43–79 years); the median age for the COAD group was 42 years (IQR 25–60 years), and that for the LOAD group was 77 years (IQR 65–85).

The female-to-male ratio was similar in both groups and showed a tendency toward male dominance, but the differences were not significant. In the COAD group, there were 11 men and 9 women (55 and 45%, respectively, 1:1.22), and in the LOAD group, 50 men and 37 women (57.5 and 42.5%, respectively, 1:1.35).

Ethnicity

The ethnic composition of the LOAD group was as follows: 32 (49.2%) Ashkenazi Jews, 31 (47.7%) Sephardic Jews, and 2 (3.1%) of other origin (one Arab and one Indian). The ethnic composition of the COAD group was 50% Ashkenazi Jews, 42.9% Sephardic Jews, and 7.1% of other origin (one Ethiopian). No significant ethnic differences were found between the two groups. An examination of skin type using the Fitzpatrick scale (which ranges from 1 to 6, in which lower numbers correspond to lighter skin and higher numbers to darker skin) showed that among the LOAD patients, 20 had skin type 1 or 2, 15 had

Table 2. Clinical characteristics of the patients

	COAD, <i>n</i> (%)	LOAD, <i>n</i> (%)	<i>p</i> value
Itch severity			
Mild	10 (50)	45 (52)	ns
Severe	10 (50)	42 (48)	ns
Area of skin involvement			
Head and neck	14 (70)	41 (47.1)	ns
Ear and retroauricular fold	3 (15)	6 (6.9)	ns
Trunk	18 (90)	73 (83.9)	ns
Upper limbs	19 (95)	83 (95.4)	ns
Lower limbs	19 (95)	80 (92)	ns
Palms and soles	6 (30)	20 (23)	ns
Flexures	8 (40)	11 (12.6)	0.008
Dennie-Morgan fold	6 (30)	2 (2.3)	>0.001
Additional morphology characteristics			
Follicular accentuation	4 (20)	3 (3.4)	0.022
Nummular eczema	2 (10)	7 (8)	ns

COAD, childhood-onset atopic dermatitis; LOAD, late-onset atopic dermatitis; ns, no significance. Data are presented in numbers (%).

skin type 3, and 11 had type 4 or 5. In the COAD group, 7 patients had skin type 1 or 2, 7 patients had skin type 3, and 2 patients type 4 or 5 (Table 1).

Comorbidities and Atopy

With regard to comorbid diseases, dyslipidemia (31%), diabetes (21.8%), and hypertension (48.3%) showed a tendency of higher incidence among the LOAD patients, though no statistical significance between groups was observed. The prevalence of personal or family history of atopy was lower in the LOAD group than in the COAD group.

Patch Test

Patch testing was done in 31 patients – 23 from the LOAD group and 9 from the COAD group. Positive results were found in 6 of the 23 LOAD patients and in 1 of the 9 COAD patients. These results were not relevant to the atopic rash and were not considered as a cause of contact dermatitis.

Clinical Characteristics

All patients included in the study were classified as suffering from moderate to severe AD. All patients in both groups reported pruritus that was mild or severe; the COAD group had 10 (50%) cases of mild pruritus and 10 (50%) cases of severe pruritus, while the LOAD group had

Table 3. Laboratory findings of the patients

	COAD average (range)	LOAD average (range)	<i>p</i> value
CRP, mg/L	4.76 (0.8–13.81)	5.32 (1.63–11.16)	ns
LDH, IU/L	202 (183–273)	219.5 (190–260.25)	ns
WBC, $\times 1,000/\mu\text{L}$	7,930 (6,652–12,292)	8,000 (6,825–9,520)	ns
EOS abs, cells/ μL	225 (65–452.5)	290 (150–520)	ns
IgE, mg/dL	4,265 (448.2–14,900)	380 (91.2–1,370)	<0.001

Normal range: CRP, C-reactive protein, 0–3 mg/L; LDH, lactate dehydrogenase, 100–260 IU/L; WBC, white blood cells, $4\text{--}10.8 \times 1,000/\mu\text{L}$; EOS abs, eosinophil absolute count, 0–600 cells/ μL ; IgE, immunoglobulin E, 0–280 mg/dL. COAD, childhood-onset atopic dermatitis; LOAD, late-onset atopic dermatitis; ns, no significance.

45 (52%) cases of mild pruritus and 42 (48%) cases of severe pruritus. Among the clinical symptoms, there was a significantly higher incidence of flexural eczema and Dennie-Morgan folds in the COAD group as compared to the LOAD group (Table 2). In addition, in the COAD group there was a tendency toward more frequent head and neck involvement, but it was not found to be statistically significant. Out of the less frequent clinical types of skin eruptions, the most prevalent type was nummular eczema in both groups. The COAD group had a higher incidence of eruption with follicular accentuation.

Laboratory Data

Laboratory parameters such as lactate dehydrogenase, C-reactive protein, white blood cell count, and eosinophil count showed no differences between the two groups (Table 3). However, total serum IgE levels were significantly higher in COAD patients than in LOAD patients (mean value of 4,265 mg/dL and 380 mg/dL for COAD and LOAD, respectively).

Treatment Modalities and Response

All patients were treated with topical agents. Of the patients treated with phototherapy, in the LOAD group, 42 of 46 (78%) patients responded to treatment, while in the COAD group, 8 of 13 (61.5%) patients responded. This difference was statistically significant ($p = 0.019$). Of the patients treated with methotrexate, in the LOAD group, 12 of 13 (92%) treated patients responded, and in the COAD group, 4 out of 6 (66%) responded. Although there was a tendency toward better treatment response in the LOAD group, it was not found to be statistically significant. Other treatments showed no significant differences between the groups.

Discussion

In the framework of this study, we have examined a cohort of single-center hospitalized adult patients with AD; these patients were divided into subgroups of COAD and LOAD in order to characterize differences in demographic, clinical, and laboratory data, as well as response to treatment between these groups.

Most patients in the study group (81%) had LOAD. This proportion of LOAD in adult AD is higher than that reported in the previous literature, wherein the average proportion of LOAD patients is reported to be 26%, with a range of 16.5–53%. The highest proportion of AD patients presenting with LOAD was reported in the USA, with a mean of 53% (range 51.8–54.1%), while in Europe it was 24% (range 13.6–36.3%), in Asia 21.4% (range 18.2–38.7%), and in other regions 24.3% (range 0.2–69.2%) [6]. There are several possible explanations for the high proportion of LOAD patients in our study. First, our study included only hospitalized patients, and younger adult patients tend to avoid hospitalization due to loss of working days and responsibility for child care, and thus prefer to be treated on an ambulatory basis. Therefore, the patients in the present study were older than those of previous reports that focused on ambulatory populations. Another possible explanation is that younger COAD patients better comply with treatments and manage better with ambulatory care than older LOAD patients. Alternatively, it is possible that AD in elderly patients is less responsive to self- or ambulatory treatments and, thus, more frequently requires hospitalization.

Beyond the relatively old age in the study population, there was a statistically significant difference in median age between COAD (42 years) and LOAD (77 years) groups. It should be noted that several previous studies showed that LOAD onset was equally distributed across all ages [6, 9, 10]. The age differences in our study may again be related to the fact that the present study evaluated hospitalized patients. Additionally, COAD patients have a prolonged history of the disease, which may lead to disease hardening at younger age and high prevalence of severe cases when patients reach their 40s, while LOAD patients are exacerbating in much older ages.

The female-to-male ratio in our study was similar in both groups and showed a tendency toward male dominance (1:1.22 in COAD and 1:1.35 in LOAD), but the differences were not statistically significant. Several previous studies reported the proportion of COAD and LOAD by gender and showed no differences between females and males [11, 12]. Other studies have found a higher in-

cidence of AD in women; some researchers explained this phenomenon as being due to the ability of estradiol to exacerbate T-helper 2 response and promote mast cell degranulation, and the fact that dehydroepiandrosterone has a protective effect against T-helper 2 disorders [13, 14]. Although no statistical significance was found with regard to gender differences in our study, if some meaning is to be ascribed to these differences, we attribute them again to the hospitalization issue; there may be a higher incidence of moderate to severe disease in men. Another possibility is that men with moderate to severe disease are less likely to manage with ambulatory care during exacerbations.

It was described previously that the incidence of AD varies across diverse ethnic groups, occurring more frequently in Asian and black individuals than in whites. Previous research has shown that there are differences in genetic polymorphisms that influence susceptibility to AD, disease phenotype, and response to different therapies [15]. Our study did not demonstrate significant differences in ethnicity (either ethnic origin or Fitzpatrick skin type) between COAD and LOAD. Most patients included in the study were white Jews of different descent (Ashkenazi and Sephardic), who represent a special ethnic subgroup with their genetic and geographic characteristics. Therefore, this study contributes uniquely to the understanding of AD symptomatology and epidemiology.

A high incidence of family and personal history of atopy was observed in all our patients but was significantly higher in COAD. In the previous literature, the association of COAD and LOAD patients with different types of atopy has been inconclusive. While most studies have shown a higher incidence of atopy in COAD, others found no differences between groups, and there are some that described a higher frequency of certain types of atopy in LOAD patients [6, 10–12, 16].

As described in the literature, with advancing age, there is a decrease in the frequency of various atopic phenomena. Therefore, we attribute the lower incidence of atopy in LOAD patients in this study to the age differences between the groups (our LOAD patients were significantly older than the COAD patients).

Recently, several studies have shown that, similar to psoriasis, AD is a chronic inflammatory disease considered to be a systemic disorder with many comorbidities, especially atherosclerosis [17, 18]. In a study published by Megna et al. [11], the most frequent comorbidity found in LOAD patients was hypertension. These authors also reported a high incidence of dyslipidemia, diabetes, and

thyroiditis in the LOAD group [11]. In agreement with the previous literature, our study showed a high prevalence of several comorbid diseases in both COAD and LOAD patients. A higher incidence of dyslipidemia, diabetes, and hypertension was found in LOAD patients, as compared to COAD patients, though no statistical significance in differences between groups was observed.

Several previous studies have described the morphology and distribution of skin eruption in COAD and LOAD patients [8], and results differ between researchers. Not all studies found differences between groups. However, certain patterns of clinical features were consistently found in several studies. There is a higher proportion of facial and eyelid involvement, flexures, and Dennie-Morgan lines in COAD as compared to LOAD. By contrast, there is a higher proportion of foot, hand, and trunk involvement in LOAD as compared to COAD. Erythematous desquamative (eczematous) lesions are a common morphological pattern described in both groups. Less common morphological variants, such as nummular or prurigo-like lesions, were described more frequently in LOAD. A link was also reported between ethnic group and the morphology of the skin lesions. It was reported that in patients with darker-colored skin, erythema is less obvious, and these patients frequently present with follicular, papular, or lichenoid eczema and prurigo nodularis [6, 9–12, 19]. Similarly to the prior literature, the present study found a significantly higher incidence of flexural eczema and Dennie-Morgan folds in the COAD group. As opposed to some previous reports, nummular eczema was found with a similar frequency in both groups, and there were more cases of follicular eczema in COAD cases. These differences between groups may be related to the differing ethnic groups included in the present study.

Different pathways of immune activation in AD have been suggested [13]. AD has been categorized into two types: extrinsic (IgE-allergic) and intrinsic (non-IgE-allergic) AD. Patients with extrinsic AD demonstrate high total serum IgE level and the presence of IgE antibodies specific to environmental and food allergens, whereas patients with intrinsic AD exhibit normal total IgE and an absence of allergen-specific IgE antibodies. It has been reported that the extrinsic form of AD is associated with the loss-of-function mutations in the FLG gene that are one of the major AD risk factors [20]. These mutations were found in COAD patients, corresponding to a severer clinical course of the disease. These patients are at increased risk for developing all other forms of, and complications with, atopy later in life. Clinically, intrinsic AD has a relatively late onset and is more common in

elderly patients. It was estimated that out of all AD patients, about 70–80% demonstrate the extrinsic type [21]. It should be noted that there is overlap between the two forms of AD, as sometimes the intrinsic form later becomes the extrinsic form. The majority of patients in both groups in the present study showed increased serum IgE levels together with increased atopic background, which indicates a predominance of the extrinsic type of AD, similar to reports of previous literature. A number of studies have described an age-related decline in IgE, which is an important factor in the pathogenesis of AD, in conjunction with a decrease in atopy [22]. In the present study, LOAD patients were significantly older than COAD patients, and therefore, the lower values of total serum IgE found in the LOAD patients in this study are in agreement with the existing data [10, 23, 24].

In evaluating response to treatment, we found that LOAD patients had a better response to phototherapy. Treatment response was observed in 42 patients with LOAD (91.3%) but only in 8 patients (61.5%) with COAD. Our patients were treated with narrow-band ultraviolet B light, which is considered to be the first-line phototherapeutic option for moderate to severe AD [25–27]. It is known that in comparison to psoriasis, AD in general responds less reliably to phototherapy. There are still a reasonable number of patients who do not respond, or even get worse, under phototherapy. In contrast to chronic plaque-type psoriasis, AD is now understood to be a much more heterogeneous disease, with activation of Th22, Th17/IL-23, and Th1 cytokine pathways depending on the subtype of the disease. It was shown that clinical disease resolution in patients with chronic AD is accompanied by reversal of both the epidermal defects and the underlying immune dysregulation; this reversal in immune dysregulation expresses itself via resolved Th2 and Th22 inflammation. The lower efficacy of phototherapy in COAD patients may be related to several factors, including differences in immune dysregulation and involvement of difficult-to-reach areas that can also be less responsive to ultraviolet light (e.g., the head, genitals, and skin folds). In addition, COAD patients have a long-lasting disease and some of them have been treated with phototherapy in the past; it has been described that long-term phototherapy treatments often cease to work, even if there was initially a good response [28].

The main limitation of our study is the fact that it was a retrospective study from a single tertiary center. This could have led to a selection bias of a subgroup of severer atopic patients who failed ambulatory treatment and needed hospitalization.

In conclusion, we found that, as in ambulatory adult patients with AD, there are significant differences in the medical background, clinical and laboratory characteristics, and response to treatment between hospitalized LOAD and COAD patients. LOAD patients are older, have a lower incidence of family or previous personal atopic background, and show different clinical characteristics, with less frequent involvement of skin folds and eyelids, lower IgE levels, and better response to phototherapy. The AD criteria defined by Hanifin and Rajka are not optimal for diagnosing adult AD. There is a need to determine new diagnostic criteria and treatment guidelines for both groups.

Key Message

There are differences in background, clinical, laboratory, and treatment response between late-onset and childhood-onset atopic dermatitis in adult hospitalized patients.

Statement of Ethics

The study was approved by the local ethical committee.

Disclosure Statement

The authors have no conflicts of interest to disclose. There was no funding source for this work.

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Patients and Methods

The computerized medical records of adult atopic dermatitis (AD) patients who were hospitalized at the dermatology department and followed in the outpatient clinic of Sheba Medical Center between 2009 and 2017 were reviewed for this study.

All patients in the study were adults, aged 18 years and above. Pregnant women were excluded.

Detailed medical and medication histories were obtained from all participants. Diagnosis of AD was determined through the presence of a pruritic eczematous eruption with a chronic or chronic-relapsing course lasting at least 6 months that could not be attributed to other eczematous or eczema-mimicking conditions. In all biopsies performed (89 out of 107 cases), the diagnosis was supported by histological findings demonstrating acute, subacute, or chronic eczematous dermatitis with varying degrees of spongiosis or psoriasiform dermatitis and presence of inflammatory infiltrate-containing eosinophils. Cases with the presence of necrotic keratinocytes, which may suggest an irritant contact dermatitis in the pathogenesis, and cases with histological findings suggestive of other conditions (e.g., cutaneous T-cell lymphoma) were all excluded, as other diagnoses could not be ruled out in these cases. To minimize the possibility of unrecognized contact dermatitis or urticarial-stage bullous pemphigoid, patch tests and direct immunofluorescence tests were performed when needed, based on clinical judgment. Personal or family history of atopy and IgE level were documented but were not considered to be diagnostic criteria.

The subjects with AD were classified as COAD and LOAD based on the age of onset of the disease (<18 or ≥ 18 years, respectively). Evaluated characteristics included: the age of onset; sex; ethnicity; skin type according to the Fitzpatrick scale for human skin color; medical history; personal or familial atopic background; and clinical characteristics, laboratory data, and response to treatment. Atopy characteristics included symptoms other than dermatitis, such as family history of atopy, personal history of asthma, allergic rhinitis, conjunctivitis, and various allergies, including drug allergy and positive patch test with no clinical relevance. Clinical characteristics examined included the area affected by the skin eruption (head and neck, ear and retroauricular fold, trunk, upper limbs, lower limbs, palms, and/or soles), type of skin eruption (eczematous, follicular accentuation, or nummular),

and itch severity. Laboratory characteristics evaluated included C-reactive protein, lactate dehydrogenase, IgE, and white blood cell count. Only cases with complete clinical and epidemiological data, in which the differentiation between COAD and LOAD could be determined with absolute certainty, were included.

Evaluation of response to treatment included phototherapy and other systemic treatments. Response to treatment was divided into no response and partial/complete response.

The study was approved by the local ethical committee.

Statistical Analysis

Categorical variables were reported as both numbers and percentages. Continuous variables were evaluated in comparison to the normal distribution using histograms and reported using median and interquartile range (IQR). Comparison of categorical variables was conducted between the groups using χ^2 and Fisher's exact tests. Continuous variables were compared between groups using the Mann-Whitney test. All statistical tests were two-sided. The significance value $p < 0.05$ was defined as statistically significant. SPSS software was used for all statistical analyses (IBM SPSS statistics ver. 24, 2016, IBM Corp., Armonk, NY, USA).