

Clinical Features of Antinuclear Antibody-positive Patients with Atopic Dermatitis

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Abstract

Twenty to thirty percent of patients with atopic dermatitis (AD) are positive for antinuclear antibodies (ANAs). In this study we investigated the prevalence of ANA in 100 patients with AD and examined the difference between ANA-positive (ANA (+)) and ANA-negative (ANA (-)) patients with AD. ANAs were identified with indirect immunofluorescence on Hep-2 cells. Nineteen patients (19%) with AD were found to be positive for ANAs at titers ranging from 1 : 40 to 1 : 640. The rate of ANA positivity in male patients (20.4%) was higher than that in female patients (17.6%). The rate of ANA positivity differed significantly between patients with AD and healthy control subjects ($p=0.0001$, odds ratio: 2.8). There was also a relationship between ANA (+) AD and photosensitivity in male subjects ($p=0.0346$). The ANA (+) patients with AD showed higher levels of cedar pollen-specific IgE than did ANA (-) patients ($p=0.0232$). In ANA (+) patients disease severity was correlated with basophil counts ($r=0.513$, $p=0.0344$) and serum LDH levels ($r=0.741$, $p=0.0056$). The results indicate that patients with AD who are positive for ANA are a subpopulation of patients with AD.

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Key words: antinuclear antibodies, atopic dermatitis, basophils, photosensitivity, disease severity

Introduction

Atopic dermatitis (AD) is a common, chronic, relapsing inflammatory skin disease featuring severe pruritus and typical cutaneous symptoms¹. Patients with AD are a heterogeneous group of whom 80% show immediate-type skin reaction and elevated serum IgE levels. Atopic diseases, such as AD, are generally considered to be due to hyperresponsiveness to exogenous antigens,

whereas autoimmune diseases are thought to be due to hyperresponsiveness to endogenous antigens. Several autoantibodies that have been categorized as IgE class or IgG class have been detected in patients with AD²⁻⁶. Varenta et al have reported IgE-class autoantibodies, Hom s 1-5, and anti-Hom s 1 antibodies show a prominent reaction in the epidermis from lesional skin of patients with AD⁴. In addition, circulating immune complexes, such as Hom s 1-IgE and Hom s 3-IgE, have been detected in sera from patients with AD^{7,8}, and anti-elongation

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factor-1 alpha autoantibodies and anti-LEDGF/p75 antibodies have been reported as IgG-class autoantibodies in patients with AD^{5,6}. Twenty to thirty percent of patients with AD are positive for antinuclear antibodies (ANAs)⁹⁻¹¹. A previous study has demonstrated that patients with AD who have facial lesions tend to have high titers of ANA^{9,10}. However, there are a few detailed reports of the clinical evaluation of patients with AD who are ANA-positive (ANA (+)), and the role of autoantibodies in the pathogenesis of AD has not been fully elucidated. The aim of this study was to elucidate the prevalence of ANAs in patients with AD and to examine the difference between ANA (+) and ANA-negative (ANA (-)) patients with AD.

Materials and Methods

Patients and Healthy Control Subjects

One hundred patients with AD (mean age: 28.2 years; range: 2-64 years; 49 male patients [mean age: 30 years] and 51 female patients [mean age: 26.4 years]) who had visited the Nippon Medical School Main Hospital or Nippon Medical School Chiba Hokusai Hospital from October 2002 through December 2003 and who fulfilled the criteria for AD of Hanifin and Rajka were recruited for this study¹. The severity of dermatitis was graded with the criteria of Rajka and Langeland and was based on the following criteria: extent ("rule of nine"), course (by history), and intensity (disturbance of night sleep by itching)¹². The total score ranged from 3 to 9 points, and the disease severity was classified as mild (3 or 4 points), moderate (5-7 points), or severe (8 or 9 points). The severity of facial lesions was also graded on the basis of the extent of facial eruptions (erythema, papules, erosions, and lichenification), and the facial disease severity was classified as mild (less than 30%), moderate (30%-60%), or severe (more than 60%). We excluded patients who had a history of ultraviolet (UV) therapy. Photosensitivity was assessed by interview. Informed consent was obtained prior to inclusion in the study, and Institutional Review Board approval was granted. The rate of ANA positivity in 1,004 healthy control subjects (mean age: 48.8 years; range: 20-70 years;

411 men [mean age: 47.3 years] and 593 women [mean age: 49.7 years]) was determined by SRL, Inc. (Tokyo). Healthy control subjects had no active diseases and no history of allergic conditions, such as bronchial asthma and AD.

Laboratory Investigations

Laboratory examinations, including determinations of complete blood count, differential white blood count, serum lactate dehydrogenase (LDH) were performed. Total serum IgE levels, and the level of specific IgE antibodies to environmental antigens (orchard grass, ragweed, cedar pollen, *Candida albicans*, *Malassezia*, cat dander, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust) were tested by fluorescence enzyme immunoassay. Antibodies to double-stranded DNA, Ro/SS-A, and La/SS-B were measured with enzyme-linked immunosorbent assay in ANA (+) patients with AD. Total hemolytic complement titers (CH50) were also examined in these patients.

ANA Measurement

ANAs were identified with indirect immunofluorescence on Hep-2 cells fixed in acetone using serum diluted in phosphate-buffered saline and fluorescein-isothiocyanate-conjugated rabbit anti-human immunoglobulins (mixture of IgG, IgM, and IgA). A titer of 1 : 40 or higher was considered to indicate ANA positivity.

Statistical Analysis

Statistical analysis was performed with Wilcoxon's signed rank test or Spearman's rank correlation test for paired data and with the Mann-Whitney *U*-test for unpaired data. The percentage of ANA (+) patients with AD and the photosensitivity results were analyzed with Fisher's exact probability test. Differences associated with a probability of $p < 0.05$ were considered statistically significant.

Results

ANA Positivity in Patients with AD and Healthy Control Subjects

Nineteen (19%) patients with AD were ANA (+) at

Table 1 ANA in male and female patients with AD

		ANA titer							total
		0	20X	40X	80X	160X	320X	640X	
AD	Male (%)	37 (75.5)	2 (4.1)	6 (12.2)	2 (4.1)	1 (2)	0	1 (2)	49
	Female (%)	37 (72.5)	5 (9.8)	6 (11.8)	3 (5.9)	0	0	0	51
	Total (%)	74 (74)	7 (7)	12 (12)	5 (5)	1 (1)	0	1 (1)	100
control subjects*	Male (%)	378 (92)	28 (6.8)	3 (0.8)	1 (0.2)	1 (0.2)	0	0	411
	Female (%)	459 (77.4)	71 (12)	38 (6.4)	16 (2.7)	5 (0.8)	0	4 (0.7)	593
	Total (%)	837 (83.5)	99 (9.7)	41 (4.1)	17 (1.7)	6 (0.6)	0	4 (0.4)	1,004

ANA positivity (40X–640X) in patients with AD; total: 19 of 100=19%

Male: 10 of 49 patients=20.4%; Female: 9 of 51 patients=17.6%

*ANA Positivity in control subjects. Total: 68 of 1,004 subjects=6.8%

Male: 5 of 411 subjects=1.2%; Female: 63 of 593 subjects=10.6%

titers ranging from 1 : 40 to 1 : 640 (**Table 1**). The rate of ANA positivity in control subjects was 6.8% (68 of 1,004 subjects). The ANA positivity rate differed significantly between patients with AD and control subjects ($p=0.0001$, odds ratio: 2.8). Although the rate of ANA positivity in male patients with AD (20.4%) was higher than that in female patients with AD (17.6%), and the rate of ANA positivity in female control subjects (10.6%) was significantly higher than that in male control subjects (1.2%; $p=0.0001$). The rate of ANA positivity in male patients with AD was significantly higher than that in males control subjects ($p=0.0001$, odds ratio: 17). There was no significant difference between female patients with AD and females control subjects in the rate of ANA positivity. The fluorescent patterns of 19 patients with ANA (+) AD were: homogeneous type in 9 patients, homogeneous and speckled type in 7 patients, speckled and other type in 2 patients, and speckled and nucleolar type in 1 patient. None of the 19 patients with ANA (+) AD showed anti-DNA antibodies, anti-Ro, anti-La, or decreased CH50 levels. They had no signs or symptoms of systemic lupus erythematosus (SLE).

Relationship between ANA and Photosensitivity in Patients with AD

Patients with AD and photosensitivity tended to

be ANA (+) ($p=0.0524$; **Table 2**). There was a relationship between ANA positivity and photosensitivity in male patients with AD but not in female patients ($p=0.0346$ and $p=0.387$, respectively; **Table 2**).

Disease Severity in ANA (+) and ANA (–) Patients with AD

The rates of both severe AD and severe facial AD were slightly but not significantly higher among ANA (+) patients than among ANA (–) patients (disease severity: 28% vs. 17.8%; facial disease severity: 18.2% vs. 12.3%; **Fig. 1**). Furthermore, titers of ANA were not significantly higher in patients with severe AD or severe facial AD than in other patients. We also examined the disease severity in the ANA (+) and ANA (–) patients according to sex, there was no difference between ANA (+) AD and ANA (–) AD in both male and female patients with AD (data not shown).

Comparison of Laboratory Data between ANA (+) and ANA (–) AD

No significant differences were observed between ANA (+) and ANA (–) patients with AD in complete blood count, differential white blood count, serum LDH levels, total serum IgE level, sex, or age (data not shown). Furthermore, we examined the levels of

Table 2 Relationship between ANA and photosensitivity in patients with AD

all patients		Photosensitivity		
		(+)	(-)	
ANA	(+)	5 *	6	11
	(-)	10	48	58
		15	54	69

**

Male		Photosensitivity		
		(+)	(-)	
ANA	(+)	3	4	7
	(-)	2	29	31
		5	33	38

#

Female		Photosensitivity		
		(+)	(-)	
ANA	(+)	2	2	4
	(-)	8	19	27
		10	21	31

##

*: The number of patients
 **: p=0.0524 (Fisher's exact probability test)
 #: p=0.0346
 ##: p=0.387

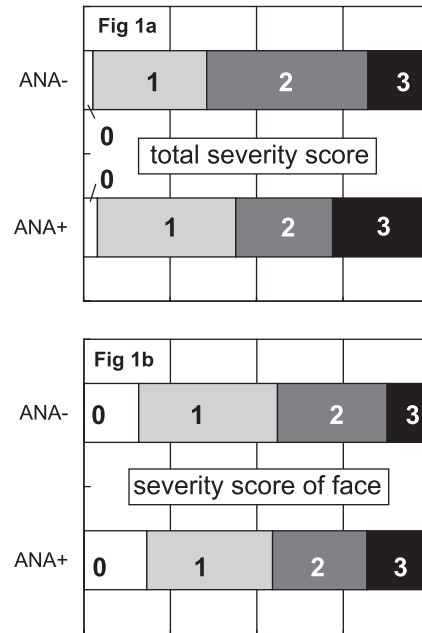


Fig. 1 Distribution of percentage of severe, moderate and mild AD in positive-ANA (ANA+) and negative-ANA (ANA-) patients. Classified by disease severity (Fig. 1a), by disease severity of the face (Fig. 1b) (Severe=3, Moderate=2, Mild=1, No eruption=0)

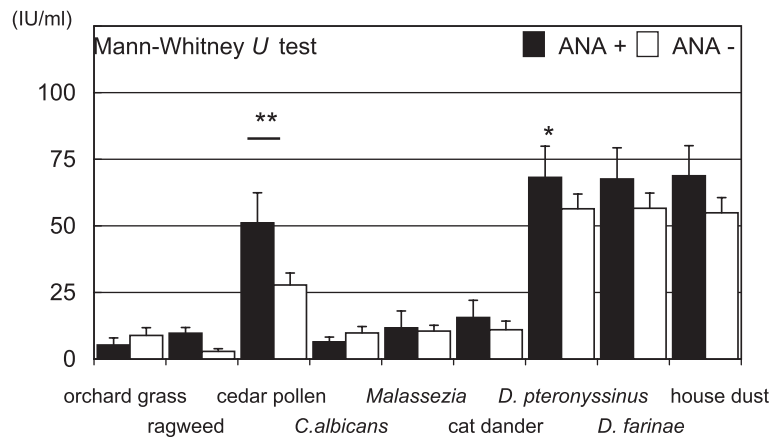


Fig. 2 The level of specific IgE Abs to environmental Ags in ANA+ and ANA- patients with AD (excluded patients with normal range of IgE levels (<150 IU/mL)). *: Results are expressed as mean ± the standard error of the mean (SEM), **: p=0.0232

IgE antibodies specific for environmental antigens in both groups, except in patients with IgE levels within the normal range (<150 IU/mL; Fig. 2). The ANA (+) patients with AD showed higher levels of cedar pollen-specific IgE than did ANA (-) patients with AD (p=0.0232), but there was no statistical

correlation between ANA titer and the levels of cedar pollen-specific IgE, nor was there any significant correlation between total IgE levels and the levels of cedar pollen-specific IgE in ANA (+) patients with AD (data not shown). In addition levels of both cedar pollen-specific IgE and ragweed-

Table 3 The correlation between severity score and immunological parameters

		WBC	neutrophil	eosinophil	basophil	monocyte	lymphocyte	platelet	IgE	LDH
ANA (-) AD n=74	Severity score	r 0.418	0.285	0.505	0.035	0.288	- 0.037	0.272	0.342	0.419
		p 0.0004	0.0163	<0.0001	ns	0.0152	ns	0.0219	0.0054	0.0012
ANA (+) AD n=19	Severity score	r 0.221	0.046	0.187	0.513	0.25	0.129	- 0.092	0.01	0.741
		p ns	ns	ns	0.0344	ns	ns	ns	ns	0.0056
total AD n=100	Severity score	r 0.37	0.231	0.45	0.157	0.271	0.025	0.187	0.24	0.493
		p 0.0003	0.0237	<0.0001	ns	0.0079	ns	ns	0.022	<0.0001

The correlation between disease severity score and immunological parameter was analysed using Spearman's rank correlation test.

ns: no significance

specific IgE were higher in ANA (+) female patients with AD than in ANA (-) female patients with AD ($p=0.0066$ and $p=0.0097$, respectively) but did not differ in male patients with AD.

In ANA (-) patients with AD, disease severity was correlated with several immunological variables (**Table 3**), such as white blood cell counts ($r=0.418$ and $p=0.0004$), eosinophil counts ($r=0.505$ and $p<0.0001$), and serum LDH levels ($r=0.419$ and $p=0.0012$). However, in ANA (+) patients with AD disease severity was correlated with basophil counts ($r=0.513$ and $p=0.0344$) and serum LDH levels ($r=0.741$ and $p=0.0056$). In all patients with AD, disease severity was correlated with eosinophil counts ($r=0.45$ and $p<0.0001$) and serum LDH levels ($r=0.493$ and $p<0.0001$).

Discussion

In the present study we found that 19% of patients with AD were ANA (+) and that this rate was much higher than that in healthy control subjects ($p=0.0001$; odds ratio: 2.8). In addition, ANA (+) patients with AD tended to have photosensitivity ($p=0.0524$) and showed high levels of cedar pollen-specific IgE ($p=0.0232$). Furthermore, male patients with AD (20.4%) were more likely than female patients (17.6%) to be a positive ANA (+). The rate of ANA positivity in male patients with AD was significantly higher than that in male control subjects ($p=0.0001$, odds ratio: 17), and although we divided patients into those with photosensitive AD and those with nonphotosensitive AD only on the

basis of interview and not on the basis of minimum erythema dose, were found an association between ANA positivity and photosensitivity in male patients ($p=0.0346$). Japanese investigators have previously found that 10.5% to 34% of patients with AD are ANA (+) and that patients with AD who have facial lesions tend to be ANA (+)^{9-11,13}. We were not able to find a correlation between ANA positivity and severe facial lesions in our patients with AD. The rate of ANA positivity in AD varies widely in previous reports owing to differences in technical procedures and the ages of patients. Tada et al have concluded that ANA must be investigated to differentiate autoimmune diseases in females from photosensitive female AD patients with severe facial lesions⁹. Interestingly, Ginel et al have reported that facial lesions are more common in ANA (+) dogs with AD (25%) than in ANA (-) dogs with AD¹⁴.

In this study, we could not find any other autoantibodies, such as, double-stranded DNA antibodies, anti-Ro antibodies, and anti-La antibodies, in patients with ANA (+) AD; however, we have previously reported on 2 male patients with AD complicated by SLE¹⁵. We believe that it is rare for AD to be complicated by SLE. Arbuckle et al have reported that autoantibodies are typically present many years before the diagnosis of SLE and that ANAs (at a dilution of 1 : 120 or more) are present before diagnosis in 78% of patients with SLE¹⁶. One female patient in our study had only facial lesions, no systemic involvement, and a history of AD. Thus, she was suspected of having AD but had a high titer of ANA (1 : 640, speckled type) and no history

of photosensitivity. Although the lupus band test was positive, other immunological findings were absent. Therefore, cutaneous lupus erythematosus was diagnosed. Dermatologists may sometimes mistake mild hydropic degeneration of the basilar epithelial layer for eczematous change. When evaluating patients with such symptoms, physicians should obtain a complete history and measure the serum ANA titer. In addition, the beneficial therapeutic effects of UV radiation, such as psoralen plus UVA phototherapy, UVA-1, and narrow-band UVB, on AD are well known¹⁷. Although it was very rare for AD to be complicated by SLE, serum ANA levels should be examined before phototherapy is performed.

Tada et al have reported finding no significant differences between ANA (+) and ANA (-) patients with AD in eosinophilia, total serum IgE levels, specific IgE antibodies to *D. pteronyssinus*, photosensitivity, disease duration, or associated respiratory atopy¹⁰. However, Tada et al did not analyze cedar pollen-specific IgE antibodies in either the ANA (+) or ANA (-) AD groups. We also attempted to clarify the differences between ANA (+) and ANA (-) patients with AD. Interestingly, levels of cedar pollen-specific IgE were higher in ANA (+) patients with AD than in ANA (-) patients with AD ($p=0.0232$), especially in female patients ($p=0.0066$), but there was no correlation between ANA titer and levels of cedar pollen-specific IgE in ANA (+) patients with AD. It is unclear why ANA (+) patients with AD had high levels of cedar pollen-specific IgE. In Japan, cedar pollen is the most prevalent environmental antigen. To date there has been no report from other countries on the rate of ANA positivity in patients with AD, so we cannot say whether ANA (+) patients with AD in countries other than Japan have high levels of cedar pollen-specific IgE. Our findings suggest that ANA (+) patients with AD easily produce a specific IgE to the most prevalent environmental antigen. We suspect that there is an aberrant function of B cells that causes them to produce both an ANA and an IgE class of environmental antigens in ANA (+) patients with AD.

Moreover, analysis of the correlation between

disease severity and immunological variables revealed that patterns differed between ANA (+) and ANA (-) patients with AD. The severity of AD is generally believed to be correlated with eosinophil counts and serum LDH levels^{18,19}. Furthermore, our results for all patients with AD indicate that disease severity is correlated with eosinophil counts ($r=0.45$) and serum LDH levels ($r=0.513$; **Table 3**). However, the disease severity scores of ANA (+) patients with AD correlated with basophil counts ($r=0.513$) and serum LDH levels ($r=0.741$) but did not correlate with eosinophil counts. Basophils, which represent less than 1% of peripheral blood leukocytes, express FcεRI on their surfaces and can be activated to produce an array of allergic chemical mediators upon crosslinking of FcεRI-bound IgE-Ags complexes²⁰⁻²². Basophils are also a major source of Th2 cytokines, such as interleukins 4 and 13²³⁻²⁵. Recently, Mukai et al have reported that development of chronic allergic inflammation is induced by basophils through FcεRI-IgE-antigen complexes independent of T cells and mast cells in a mouse model²⁶. Thus, the role of activated basophils in the skin inflammation of ANA (+) patients with AD should be investigated. We conclude that ANA (+) patients with AD are a subpopulation of patients with AD due to several differences from ANA (-) patients with AD, such as the classification between extrinsic AD and intrinsic AD according to the serum IgE levels and the presence or absence of allergen-specific IgE.

The prevalence of ANAs generally increases with age²⁷. A study in a rural population by Hooper et al has found a gradual increase in prevalence from about 2% at 21 to 30 years to nearly 14% at 71 to 75 years²⁷. Szakos et al have reported that 14% of 72 children with AD (mean age, 8 years) were ANA (+) and that there was no significant difference in the prevalence of ANAs between children with AD and healthy controls²⁸. However, a limitation of our present analysis is that we could not analyze age-matched ANA positivity between patients with AD and control subjects. The mean age of control subjects (48.8 years) was significantly greater than that of patients with AD (28 years). However, our data indicate an increased prevalence of ANAs in

adults with AD, especially in men (**Table 1**). In addition, the mean age of male patients with AD (30 years) was slightly but not significantly higher than that of female patients (26.4 years).

Although we could not explain why some patients with AD were ANA (+), we and the authors of a previous report have speculated that skin damage due to chronic and relapsing dermatitis and abnormalities of cell-mediated immunity in AD cause ANA production, especially in male patients with photosensitivity²⁹. Even though we could not find a correlation between ANA positivity and severe facial lesions in our patients with AD, other reports suggest that ANAs are an exacerbating factor in adult patients with AD. In fact, one of our male patients with AD had a high titer of ANAs (1 : 640, homogeneous and speckled type) but no other autoantibodies. He did not meet the diagnostic criteria for SLE. In spite of well-regulated treatment for AD in our outpatient clinic, controlling this patient's skin condition was difficult. Over 7 years, ANA titers in this patient have ranged from 1 : 320 to 1 : 640. We are using cyclosporine (3 mg/kg/day) to control the dermatitis in this patient. Although he is the only patient with such a case we have treated, there is a possibility that patients with severe and intractable AD have high ANA titers.

Becker and Barnes have reported that in the relationship between AD and other autoimmune diseases, such as SLE, Crohn's disease, and rheumatoid arthritis, co-localizations of autoimmune/inflammatory loci on 1p22.3-p22.1 (TGF β RIII), 3q21-q22.2 (CD80, CD86), and 19p13 suggest that underlying genetic components may not be disease- or tissue-specific but may involve shared basic mechanisms of immune regulation³⁰. Hence, it is interesting to consider this when studying the rate of other autoimmune antibodies, such as anticardiolipin IgM, anticardiolipin IgG, anti-beta₂-glycoprotein I IgG, anti-elongation factor-1 alpha autoantibody, and anti-LEDGF/p75 Ab in ANA (+) patients AD in trying to determine how autoimmune mechanisms, including ANA and other autoimmune antibodies, function in the pathogenesis of AD^{5,6,31-34}. In the future, we will investigate the relationship between the prevalence of ANA and the prevalence

of anti-LEDGF/p75 antibodies in patients with AD⁶.

Our results show that the ANA (+) patients are a subpopulation of patients with AD. It is important to carefully evaluate ANA (+) patients with AD, especially those with a high titer of ANA (greater than 1 : 160), for long periods. In addition, it is essential to examine patients with AD for ANAs, because ANAs may indicate a hidden autoimmune disease or an undeveloped autoimmune disease or both and may be an exacerbating factor in adult patients with AD^{15,16}.

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