Review

Allergic diseases in systemic lupus erythematosus: Prevalence and immunological considerations

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ABSTRACT

We attempted to obtain a deeper understanding of the relationship between systemic lupus erythematosus (SLE) and allergic diseases through comparative studies. Accordingly, we reviewed the association of both disorders and compared their immunological features based on the literature and our own findings. Recent studies (including ours) have indicated that the risk of IgE-mediated and/or associated allergic diseases is not markedly increased in SLE patients despite their more allergic family history when compared with controls, in contrast with earlier studies. This may be related to a change of the environmental factors contributing to allergy. In addition, assessment of the immunological similarities and differences between SLE and various allergic diseases seems to be useful for understanding the relationship between them.

Introduction

Allergic disorders and SLE are known to share certain immunological abnormalities, and there have been several studies on the prevalence of allergic disorders in SLE (1-6). Allergic reaction to drugs such as antibiotics are widely known to occur in SLE patients and may occasionally be related to the flare-up of this disease (7, 8). Regarding allergic diseases such as atopic dermatitis, asthma, allergic rhinitis, and allergic conjunctivitis, which are considered to be IgE-mediated and/or IgE-associated disorders (5), several reports have indicated a higher prevalence of such conditions in patients with SLE (1,2,4). In contrast, some more recent reports including our study have suggested that SLE patients do not show an increased risk of such IgE-mediated/associated allergic diseases when compared with non-SLE controls (3,5,6). Concerning the serum IgE level, there is no clear evidence of a higher level in SLE patients when compared with normal controls, although IgE levels are reported to change along with the activity of SLE (2,3,9, 10).

The relationship between allergic diseases and SLE is interesting with respect to clinical and immunological aspects of both diseases. Here we review the possible relationship between these diseases based on the literature and our own data.

Serum IgE level in SLE patients

Representative data from several studies on serum IgE levels in SLE patients are summarized in Table I. There have been no reports that the IgE level is significantly higher in SLE patients compared with normal individuals, as far as we know, possibly because of the wide range of IgE levels seen in SLE patients (Table I). On the other hand, a significant increase of IgE occurs in the active stage of SLE when compared to the level during remission (Table I, nos. 2 and 4). Elkayam *et al.* have indicated that elevation of the IgE level along with disease activity is not related to the level of other immunoglobulins such as IgG, and that IgE levels in SLE patients with nephritis are higher than in those without nephropathy (3). This suggests that IgE may be involved in the pathogenesis of SLE, particularly in patients with nephritis, and the existence of an IgE class of anti-DNA antibodies as well as the deposition of IgE in lupus nephritis appear to support this possibility (11-13). Furthermore, certain reports have suggested that serum IgE levels are not associated with the presence of allergic conditions in SLE patients (2, 9). Thus, the serum IgE concentration of these patients seems to be related to its pathogenic role in SLE rather than being related to allergy.

Table I. Serum IgE levels in SLE patients and non-SLE controls.

(Reference number)	Inactive SLE [1]	Active SLE [2]	Control [3]	Difference 1 vs 2	Difference 1+2 vs 3
1. Rebhun *et al.* (Ref. no. 9, 1983)	48.2 ± 75.4 IU/ml (n = 14)	161.3 ± 273.6 (n = 16)	60.3 ± 77.5 (n = 12)	N.S.*	N.S.
2. Mikecz *et al* (Ref. no. 10, 1985)	41.0 ± 1.21 kU/l (n = 54)	105.9 ± 1.26 (n = 41)	53.9 ± 1.18 (n = 25)	p < 0.01	N.S.
3. Sequeira *et al.*** (Ref. no. 2, 1993)	IgE >150 U;	21% in 132 SLE,	25% in 66 control	N.D.***	N.S.
4. Elkayam *et al.* (Ref. no. 3, 1995)	175 ± 53 IU/ml (n = 20)	696 ± 269 (n = 29)	N.D	p = 0.02	N.D.

*Not significant. **An IgE level > 150U was seen in 21% of SLE patients (n = 132) and 25% of controls (n = 66). ***Not described.

Table II. Prevalence of allergic diseases in SLE patients.

(Reference number)	All* diseases	Atopic dermatitis	Asthma	Allergic rhinitis	Allergic conjunctivitis
1. Sequeira *et al.* (Ref. no. 2, 1993)					
SLE (n = 132)	83 (63)**	47 (36)	11 (8)	22 (17)	N.D.
Control (n=66)	26 (39)	11 (17)	2 (3)	6 (9)	N.D.
	p < 0.0001***	p<0.01	N.S.	N.S.	
2. Shahar *et al.* (Ref. no. 4, 1997)					
SLE (n=60)	44 (56)	N.D.	28 (47)	20 (34)	16 (26.7)
Control (n=60)	N.D.	N.D.	3 (5.9)	8 (13.6)	8 (9.5)
3. Morton *et al.* (Ref. no. 5, 1998)					
SLE (n=49)	24 (49)	4 (8.2)	4 (8.2)	11 (22.4)	N.D.
Control (n=98)	50 (51)	8 (8.2)	8 (8.2)	14 (14.3)	N.D.
	N.S.	N.S.	N.S.	N.S.	
4. Our data (2002)**** (Ref. no. 6, 2002)					
SLE (n = 52)	11 (23)	3 (6)	3 (6)	7 (13)	4 (8)
Controls (n = 52)	25 (48)	8 (15)	4 (8)	18 (35)	5 (10)
	p = 0.004	N.S.	N.S.	p = 0.012	N.S.

*This includes the following four allergic diseases as well as drug, food, and insect allergies.
**( ) Percentage of allergic diseases in each population.
***Statistical differences between SLE and control subjects.
****Our data were obtained from 52 SLE patients (47 women and 5 men with an average age of 33.6±11 years) and controls matched for several conditions (race, sex, age, and region) (47 women and 5 men with an average age of 33.7±12 years).
See the legend of Table I.

Table III. Allergic disorders in the families of SLE patients and controls.

(Reference number)	All diseases	Atopic dermatitis	Asthma	Allergic rhinitis	Allergic conjunctivitis
1. Sequeira *et al.* (Ref. no. 2, 1993)					
SLE (n = 132)	72 (55)	16 (12)	33 (25)	39 (30)	N.D.
Controls (n = 66)	16 (24)	3 (5)	6 (9)	9 (14)	N.D.
	p < 0.0001	p < 0.002	p < 0.02	p < 0.02	N.D.
2. Sekigawa *et al.* (Ref. no. 6, 2002)					
SLE (n = 52)	35 (67)	14 (30)	12 (23)	20 (38)	7 (13)
Controls (n = 52)	33 (59)	8 (12)	16 (25)	22 (34)	4 (6)
	N.S.	N.S.	N.S.	N.S.	N.S.

See legends to Tables I and II.

Prevalence of allergic diseases in SLE patients and family members

Since Goldman *et al.* reported a high incidence of allergic disorders in SLE patients in 1976 (1), several statistical investigations into the prevalence of allergic and/or atopic disorders have compared SLE patients with controls (1-6). A large number of reports have supported the finding that drug allergy (especially antibiotic allergy) is common in patients with SLE (7, 8). The data from representative reports on the incidence of allergic diseases (such as atopic dermatitis, asthma, allergic rhinitis, and allergic conjunctivitis) in SLE, including our recent results, are summarized in Table II.

The prevalence of these four IgE-mediated/associated allergic diseases in SLE patients has been controversial. A recent study by Morton *et al.* has indicated that SLE patients do not have an increased risk of such allergic diseases, in contrast with previous reports (Table II, no. 3), although these investigations are not simply comparable because of differences (such as age, sex, race, and region) between the subjects. Elkayam *et al.* also concluded that patients with SLE did not show an increase of atopic disorders, although their results are not included in Table II (3). Our recent study matched SLE patients and controls as closely as possible for age, sex, race, and region, and we found that the incidence of allergic diseases in the SLE patients was lower than that in the non-SLE controls (Table II, no. 4). Interestingly, a recent investigation has revealed that the frequency of atopies is also lower in rheumatoid arthritis (RA) patients than in controls (14), although older studies found no difference in the prevalence of atopy between individuals with and without RA (15). Such a trend may have been related to an increase of allergy in the controls (non-SLE or RA) due to changes of environmental factors such as pollution and an increase of pollen, and we also cannot exclude the possibility that steroid and/or immunosuppressant therapy (especially for SLE) may inhibit the development of allergy through certain mechanisms including the regulation of steroid-mediated cytokines production (16).

The families of SLE patients has been reported to show a higher incidence of allergic diseases when compared with control families (Table III, no. 1). We found that the incidence of an allergic family history was slightly higher in SLE patients than in controls despite the lower frequency of allergic diseases in the SLE patients themselves (Table III, no. 2). Furthermore, a previous study showed that the prevalence of atopic dermatitis and asthma as well as serum IgE levels were higher in the children of mothers with SLE than in control children (17). In general, allergic individuals have a higher incidence of an allergic family history, but our data indicate that far more SLE patients do not have allergic diseases despite a positive family history. We compared 52 SLE patients and 52 controls, and found that 48% of the SLE patients versus 15% of the controls had no allergy despite a positive family history ($p = 0.001$) (6). These results raise the possibility that some factors which suppress allergy exist in SLE, perhaps based on the presence of a common genetic background between SLE and allergic diseases.

Comparison of immunological abnormalities in SLE and allergic diseases

Several immunological similarities have been suggested between SLE and allergic diseases, although SLE has been classically categorized as a representative immune complex disease and allergy is an anaphylactic disorder (18). Hyperresponsiveness or hypersensitivity to antigens are common to both diseases. Allergic patients show hyperresponsiveness to several antigens (atopens), and SLE patients frequently suffer from hypersensitivity to drugs or opportunistic infections, which may occasionally trigger the flare-up or onset of SLE (7,8,19-23). Based on findings regarding the relationship between human immunodeficiency virus (HIV) infection and opportunistic infections (this is known as immune restoration disease: IRD) (24), we have recently proposed that hyperresponsiveness to opportunistic infections and related symptoms often occur in SLE along with the normalization of immunity (including an increase of the CD4+/CD8+ T cell ratio with improvement of the disease) in patients who have inactive SLE and are on relatively low-dose steroid therapy, since the immune system may show hyperresponsiveness to non-self as well as self antigens in this disease (22, 23, 25).

Several studies of cytokines have suggested a plausible link between SLE and allergy, because the levels of interleukin (IL)-4, -5, -6, and -10 (TH-2 cytokines) are increased in both diseases (26, 27). It is possible that Th-2 type responses against common environmental atopens are responsible for triggering atopy, and that Th-2 cytokines also contribute to the development of polyclonal B cell activation and autoantibody production in SLE (16, 26).

Regarding the low prevalence of atopic disorders in RA patients (as described above), the different profiles of cytokine production in RA (a Th-1 disease) and atopy (a Th-2 disease) may be a factor, and the existence of typical atopy (a Th-2 disease) and RA in the same patient could be basically contradictory (14). In fact, improvement of atopic symptoms promoted by the onset of RA has been reported in certain patients without RA therapy (14).

Regarding peripheral blood lymphocytes (PBL), a decrease of the CD4+/CD8+ T cell ratio (CD4/CD8 ratio) and an increase of activated CD8+ T cells (as indicated by human leukocyte antigen (HLA)-DR expression) is common in SLE patients when the disease becomes more active (28, 29). In general, exogenous and endogenous antigens are recognized by CD4+ or CD8+ T cells, respectively (29-31). Recently, we reported the potentially important role of human endogenous retroviruses (HERV) such as HERV clone 4-1, which shows molecular mimicry of several autoantigens (including Sm and RNP antigens), in the pathogenesis of SLE. Increased transcription/translation of HERV clone 4-1 and serum antibodies to components of this HERV have been observed in SLE patients, but not in normal controls (31-36). A decrease of the CD4/CD8 ratio occurs in SLE, because CD8+ T cells activat-

ed by endogenous antigens (including HERV antigens) and/or cytokines such as IL-16 (which is produced by activated CD8+ T cells and uses CD4 as its receptor) stimulate CD4+ T cells and cause them to decrease, probably through apoptosis (29, 37). In fact, the CD4/CD8 ratio in SLE patients is inversely correlated with the level of HLA-DR expression by CD8+ T cells (28). In contrast, the CD4/CD8 ratio is increased in patients with allergic diseases (such as atopic dermatitis) due to an increase of CD4+ T cells related to the recognition of exogenous antigens (38). Thus, this ratio seems to reflect the process of recognizing endogenous antigens in SLE or exogenous antigens in allergic diseases,based on the differential hyperresponsiveness to such antigens that exists in these diseases. It seems possible that the coexistence of two diseases with different CD4/CD8 ratios is rare and that one type of disease normally excludes the other, as indicated in the relationship between SLE and allergic diseases (Table II, nos. 3 and 4). In fact, patients with SLE or mixed connective tissue disease (MCTD) associated with atopic dermatitis are reported to show atypical CD4/CD8 ratios in their PBL (39).

On the other hand, the immunological hyperresponsiveness that occurs in both diseases may help to explain the high incidence of allergic disorders in the family members of SLE patients.

Possible mechanism of hyperresponsiveness to antigens

Allergic diseases and SLE may be thought of as disorders that are related to the breakdown of tolerance to self or non-self antigens, in addition to the abnormal recognition of such antigens (19). Although the precise mechanism of hyperresponsiveness to self or non-self antigens in both diseases is still unclear, it may arise from an intolerant or low-tolerant state. Epigenetics refers to a mechanism of gene regulation that occurs independently of the nucleotide sequence. Cytosine methylation of the regulatory sequences of DNA is one such mechanism and is associated with the transcriptional inactivation of genes, while hypomethylation contributes to active transcription (40, 41).

DNA methylation seems to be interesting in relation to the mechanism of hyperresponsiveness in patients with SLE or allergic diseases. Previous studies have detected hypomethylation (deduced based on low methyltransferase activity) in T cell nuclear proteins from SLE patients and have shown that DNA methylation inhibitors such as 5-aza-deoxycytidine (5-aza C) can induce SLE-like autoreactivity and autoantibody production both *in vitro* and *in vivo* (42-44). DNA methyltransferase (DNMT) is the enzyme responsible for methylating DNA in mammalian cells and DNMT-1 is the first member of this family (44, 45). Our findings have also suggested that 5-aza C treatment of lymphocytes from normal individuals can increase the amount of HERV clone 4-1 messenger RNA (mRNA) along with a decrease of DNMT-1 mRNA (34, 36). In addition, expression of DNMT-1 mRNA in SLE patients is lower compared with that in normal individuals and it increases along with the improvement of disease activity (36).

It is possible that a decrease of DNA methylation enzymes is related to the facilitated activation of the transcription of other genes apart from HERV sequences, such as the genes for several cytokines and immunoglobulins. Consequently, these phenomena may result in an intolerant or low-tolerant state and lead to hyperresponsivness to exogenous and/or endogenous antigens. In allergic diseases, it is known that cell membrane dysfunction is characteristic and decreased methyltransferase activity is observed in the leukocyte membrane fraction from allergic patients (46). Furthermore, a role of gene hypomethylation has been suggested to be important for IL-4-mediated IgE production in patients with high serum IgE levels (47). Thus, hypomethylation may play a significant role in hyperresponsiveness to antigens in patients with allergic diseases as well as in those with SLE. Further investigations of epigenetic gene regulation, including DNA methylation, may provide important clues to the mechanism of hyperresponsiveness in patients with SLE and allergic diseases, as well as their family members.

Conclusion

Recent studies of the prevalence of allergic diseases in SLE patients, including ours, have revealed that the risk of allergic diseases is not so high in patients compared with non-SLE controls despite their higher prevalence of an allergic family history. This finding may be influenced by changes in the environmental factors contributing to allergies. In addition, such findings may reflect the immunological similarities and differences (such as hyperresponsiveness to antigens or the CD4/CD8 ratio) between both diseases. Furthermore, we cannot neglect a possible important role of certain hormones, especially estrogen, in the relationship between atopies and SLE (48). In order to clarify the relationship between these diseases and to obtain a deeper understanding of their clinical and pathogenetic features, further studies on their clinical and immunological aspects are needed.

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