The gender disparity of immunoreactants in lesional skin of lupus erythematosus patients

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ABSTRACT

Objectives. *The immunoreactants detected by direct immunofluorescence (DIF) from the skin of patients with lupus erythematosus (LE) were related to disease subtypes and skin morphology. Male patients presented more frequently with discoid rashes and females with malar rashes. We investigated the differences in immunoreactants in skin lesions between male and female LE patients.*

Methods. *The DIF records of 186 LE patients were reviewed and analysed.*

Results. *Among 186 patients (133 female and 53 male), 54 had cutaneous LE (CLE) and 132 had systemic LE (SLE). In the CLE group, eight of 33 (24.2%) women were DIF+ versus nine of 21(42.9%) men (p=0.23). In the SLE group, 49 of 100 (49%) women were DIF+ versus 17 of 32 (53.1%) men (p=0.84). The p-value was 0.01 when comparing DIF incidence between female CLE and SLE patients. IgM and complement component 3 (C3) were present in 84.2% and 52.6% of DIF+ female patients, respectively, and both were comparable between genders (p>0.05). However, IgG was observed only in eight of 57 female patients, and in 10 of 26 male patients (p=0.02). Among DIF+CLE patients, IgG was detected in none of the eight female versus three of nine male patients.*

Conclusions. *Detection of immunoreactants in skin had no gender bias in CLE or SLE, but among women, it was probably lower in CLE than SLE. IgM and C3 were the most frequent immunoreactants in skin with no gender disparity, whereas IgG in female patients was lower than in males.*

Introduction

Lupus erythematosus (LE) is an autoimmune disease that mainly involves women. Several clinical studies have been conducted to identify the differences between female and male patients with systemic LE (SLE). Male SLE patients more frequently have serositis and pleuritis (1-4), renal diseases (5-7), leukopenia, lymphopenia and thrombocytopenia (6, 8, 9), but they less frequently have anti-nuclear (1, 10), anti-SSA and anti-SSB (1, 11) antibodies. In terms of the differences in skin manifestations between genders, several studies have demonstrated that male SLE patients present more frequently with discoid rashes, whereas female patients present with Raynaud's phenomenon and malar rashes (1, 4, 9, 12).

Direct immunofluorescence (DIF), is a valuable technique for distinguishing LE from other similar skin injuries, by identifying antibodies and complement components deposited along the dermal-epidermal junction (DEJ). The sensitivity of DIF is partly related to the skin manifestations. It is lower in patients with purely discoid lesions (discoid LE; DLE) than in SLE patients with fewer discoid rashes, but with more annular, papulosquamous and malar rashes (13, 14). Considering the gender bias in skin manifestation, we tested whether the detection rates and the types of immunoreactants along the DEJ differed between male and female patients in SLE and cutaneous LE (CLE) groups.

Materials and methods

All the medical data in the present study were from the Department of Dermatology, Sun Yat-Sen Memorial Hospital, Guangzhou, China. The patients who were admitted to the department were from all the cities and rural areas of Southern China. The study was approved by the hospital ethics committee.

DIF has been one of the routine tests for lupus patients in our department since the early 1980s. Briefly, fresh skin samples were embedded in OCT tissue-freezing medium and cut into 0.5-μm thick sections in a cryostat. For staining, sections were brought to room temperature, washed twice with phosphate-buffered saline (PBS), and incubated with fluorescein-isothiocyanate-conjugated rabbit anti-human IgG, IgA, IgM, and complement component 3 (C3) antibodies in a humidified chamber for 30 min at room temperature. Unbounded antibodies were washed off with PBS. The sections were viewed under an ultraviolet microscope.

The DIF records from 1998 to 2009 were reviewed. The diagnosis of LE was based on the clinical findings, skin biopsy, DIF and serological tests. Patients

who fulfilled the ACR criteria were diagnosed with SLE, whereas those with skin lesions but not meeting the criteria were diagnosed with CLE. All patients with a final diagnosis of SLE or CLE and with DIF conducted on lesional skin were involved in this study. Eligible patients were divided into female and male groups. The detection rates and the types of the immunoreactants along the DEJ were compared between female and male patients.

Age was compared with an unpaired *t*-test, and all the other comparisons were made with Fisher's exact test. A *p*-value of 0.05 indicated statistical significance.

Results

Patients

Patients with a definitive diagnosis of CLE or SLE and with DIF examination conducted on lesional skin were included in this study. In total, 186 LE patients were analysed. There were 133 female and 53 male patients (F: M ratio=2.5:1). The onset age (mean ± SD) was 32.5±17.4 and 35.1±17.4 in female and male patients, respectively (p=0.26). Of the 133 female patients, 33 (25%) had CLE and 100 (75%) had SLE. Of the 53 male patients, 21 (40%) had CLE and 32 (60%) had SLE. The *p*-value in comparing the constitutions of the subtypes of LE in each gender was 0.05.

Female patients with CLE have a lower detection rate of immunoreactants than those with SLE

Of 186 patients with LE, 57 of 133 (43%) female patients were DIF+ compared to 26 of 53 (49%) male patients (p=0.51). We then stratified all the LE patients into CLE and SLE groups. In the CLE group, eight of 33 (24%) women were DIF+ compared to nine of 21 male patients (43%) (p=0.23). In the SLE group, 49 of 100 (49%) women were DIF+, which was not significantly different from male patients (p=0.84) (Table I). However, the detection rate of immunoreactants in female patients with CLE was lower than those with SLE (p=0.01). No significant difference was detected between male CLE and SLE patients (p=0.58). Moreover, these findings directly resulted in a significant difference in the detection rate of immunoreactants between the entire group of CLE and SLE patients with the present gender proportions (p=0.02, Table I).

Table I. Detection rates of immunoreactants from skin lesions according to gender in CLE and SLE.

	CLE		SLE		
	DIF+	DIF-	DIF+	DIF-	*p*-value
Female, n (%)	8 (24)	25 (76)	49 (49)	51 (51)	0.01
Male, n (%)	9 (43)	12 (57)	17 (53)	15 (47)	0.58
Total, n (%)	17 (31)	37 (69)	66 (50)	66 (50)	0.02

CLE: cutaneous lupus erythematosus; SLE: systemic lupus erythematosus; DIF: direct immunofluorescence; NS: not significant.

Table II. Immunoreactant profile detected in skin lesions according to gender.

	Total patients	C3	IgM	IgM, C3	IgA, G, M, C3	IgG, M, C3	IgA, G, M	IgA	IgA, M, C3	IgG, M	IgA, G
Female, n	57	8	25	14	5	2	1	1	1	0	0
Male, n	26	2	9	5	5	2	1	0	0	1	1

Table III. Distribution of immunoreactants according to gender in CLE and SLE patients.

	Total Patients			CLE		SLE		
	Female (n=57)	Male (n=26)	*p*-value	Female (n=8)	Male (n=9)	Female (n=49)	Male (n=17)	*p*-value
IgA	8	7	0.22	1	1	7	6	0.08
IgG	8	10	0.02	0	3	8	7	0.047
IgM	48	23	0.74	7	8	41	15	1.00
C3	30	14	1.00	3	5	27	9	1.00

CLE: cutaneous lupus erythematosus; SLE: systemic lupus erythematosus.

Female patients have a lower detection rate of IgG in lesional skin than male patients

The profile of the immunoreactants detected from the lesional skin is listed by gender in Table II. The most frequent pattern of immunoreactants in skin was IgM alone in both female and male patients. Other high-frequency patterns in both groups were C3 alone, coexistence of IgM and C3, and coexistence of IgA, IgG, IgM and C3 (Table II). We calculated the frequencies of each kind of immunoreactant and analysed the differences between female and male patients. Interestingly, IgG deposition in the skin was observed in only eight of 57 (14%) female patients, whereas it was present in 10 of 26 (38%) male patients (p=0.02, Table III). The higher detection of IgG in male compared with female patients was seen in both the CLE and SLE groups. Moreover, among the CLE group, IgG was detected in three of nine male patients, but in none of eight females. Among 17 male patients with SLE, seven (41%) had detectable IgG in the skin (p=0.047) in comparison to females (eight of 49, 16%; Table III). The presence of IgA, IgM and C3 was comparable in female and male patients.

Discussion

The present study demonstrates that the sensitivity of DIF in female patients with CLE was lower than in those with SLE. With the gender distribution in this study, the lower sensitivity of DIF in female CLE patients directly resulted in a statistical difference between CLE and SLE as counting females and males together of each subtype of LE. Therefore, the gender distribution has to be considered while interpreting the

previous reports (13, 14) and investigating factor related with the sensitivity of DIF in CLE or SLE.

Consistent with previous studies (13, 15, 16), IgM and C3 were the major antibody and complement component deposited in skin lesions in both male and female patients. Moreover, the frequencies of IgM and C3 did not differ between female and male patients. Interestingly, the frequency of IgG was lower in female than in male LE patients. We cannot explain these findings because we were unable to find any data addressing the gender association of the presence of IgG in any autoimmune diseases, by searching PubMed. One study has demonstrated that male lupus patients had a significantly lower Fc-γ receptor II distribution on monocytes and neutrophils when compared with female patients and normal individuals (17). However, this does not seem to have any link with the current study. In addition, we did not detect any difference in serum IgG between male and female patients (unpublished data). Sekigawa (18) and Zandman-Goddard *et al*. (19) thoroughly reviewed the most recent researches about the possible mechanisms of gender differences in lupus patients. Both groups discussed how oestrogen acted on B, T as well as dendritic cells and subsequently modified the production of IL-6, IL-10, interferon, tumour necrosis factor (TNF), TNF receptor superfamily member 14 (TNFRSF14) and so on. Sekigawa *et al*. (18) also provided the advanced researches on the expression of oestrogen receptors(ERs), and suggested that the abnormalities of the ERs on B and T cells lead to the hyper-responsibility to oestrogen and eventually induced SLE. Future researches may also take the advantages of the previous studies to investigate the gender bias of IgG in lupus patients.

Taken together, detection of immunoreactants in skin had no gender bias in CLE or SLE, but among women, it was probably lower in CLE than SLE. IgM and C3 were the most frequent immunoreactants in skin with no gender disparity, whereas IgG in female patients was lower than in males.

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