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Clinical Constellation of Annular Erythema Associated with Anti-Ro/La Autoantibodies

Annular erythema (AE) associated with anti-Ro (SSA) and/or La (SSB) autoantibody in patients with Sjögren syndrome (SS) or with SS/systemic lupus erythematosus overlap syndrome (SS/SLE), has recently been described in Orientals, and it may be a counterpart of annular skin lesion of the subacute cutaneous LE seen mostly in Caucasians. The author examined five Korean AE patients in respect to clinical diversity. In this small-sample study, subtle differences appeared between individual cases regarding the serologic features and the diagnoses of the disease. Among the five cases, four had circulating anti-Ro and anti-La antibodies, and one had only anti-La. Regarding the diagnosis, one was SS/SLE, two were primary SS, and the remaining two were only "AE associated with anti-Ro/La antibody". There seem to be a wide clinical spectrum in the disease expression of AE associated with anti-Ro/La autoantibody than previously thought.

Key Words: *Annular Erythema; Anti-Ro/La Antibody; Antibodies, Antinuclear; Sjögren Syndrome; Lupus Erythematosus, Systemic*

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INTRODUCTION

Annular erythema (AE) associated with anti-Ro (SSA) and/or anti-La (SSB) antibody (Ab)-positive patients with Sjögren syndrome (SS) or with SS/systemic lupus erythematosus overlap syndrome (SS/SLE), has recently been described in Japanese and Korean people (1-5). These recurrent skin lesions of AE as seen in anti-Ro/La Ab-positive patients are regarded as a unique cutaneous manifestation of SS or SS/SLE, especially in Orientals. This display can be distinguished clinically as well as histopathologically from annular erythematous lesions of subacute cutaneous LE (SCLE, a clinical subset of LE), which occurs mostly in anti-Ro/La Ab-positive Caucasian patients (however, only rarely be seen in Orientals) (6, 7). To date, not a single case of this AE developing in SS has been reported among Caucasians. The pathophysiological mechanism underlying this cutaneous manifestation is not well defined; still, there may be some racial differences in immune responses to anti-Ro/La Ab (7, 8).

The clinical spectrum of the disease expression of AE with this particular antinuclear Ab (ANA) appears to be broad and diverse. We examined five Korean cases of AE in respect to clinical heterogeneity.

PATIENTS AND METHODS

Five AE patients, associated with anti-Ro/La Ab and examined between 1996 and 1999, were selected for this study. Biopsy specimens of AE on the skin were obtained at the time of the patients' first visits. The compatible histological findings of AE were perivascular and to a certain extent, periappendageal infiltrations of lymphocytes with some neutrophils and/or plasma cells throughout the dermis, without any changes in the overlying epidermis (1, 2). The diagnosis of SS and SLE were strictly based on the 1993 and 1982 ARA criteria (9, 10), respectively.

In addition to routine laboratory tests, including complete blood counts, other relevant serological examinations were performed. These included assays for ANA (indirect immunofluorescence using Hep-2 cell substrates), anti-nDNA Ab (enzyme-linked immunosorbent assay [ELISA]), anti-Sm/U_1RNP/Ro/La Abs (gel double immunodiffusion), rheumatoid factor (RF, immunoturbimetric assay), complement profile (CH_{50}, C3/C4 concentrations), and serum protein electrophoresis.

With these five patients, cutaneous and systemic manifestations, serological abnormalities, and the diagnosis of

each patient were reviewed. Brief presentations of two of these cases are as follows.

Case 1

A 22-year-old female had AEs of 3-4 cm in diameter on the mandible area of the face for a period of 2 weeks (Fig. 1A). She was a SLE patient, who was diagnosed 1.5 years earlier (positive findings were persistent leukopenia, high titer of ANA, recurrent episodes of proteinuria, malar rash, and photosensitivity). At the time of her visit, the disease activity of SLE had somewhat declined, with only a moderate degree of malar erythema and photosensitivity. The patient had been free of ocular or oral dryness before the onset of the erythemas. Four months after the development of AEs on her face, she felt some dryness in her eyes and mouth, with an almost depleted salivary reservoir at the base of her tongue. Other than the AE facial lesions and malar rashes, physical examination revealed no other positive findings. Her past history and family history were not contributory.

Laboratory findings showed leukopenia (3,000-3,500/μL) and an elevated erythrocyte sedimentation rate of 40 mm/hr. ANA test was positive (speckled pattern at a titer of 1:2,560). Anti-Ro and anti-La Abs were present; however, Abs to nDNA, Sm, and U_1RNP were not detected. The test for RF was positive. The complement profile in the serum was normal. In the serum protein electrophoresis, a finding of polyclonal gammopathy was noted. Histologic examinations of the elevated border of AE demonstrated a moderate degree of perivascular lymphocytic infiltration throughout the dermis. A few neutrophils, eosinophils, and plasma cells were also intermingled. The lupus band test from the normal appearing extensor forearm showed fine speckled nuclear and cytoplasmic deposits of IgG in the epidermis. The Schirmer test result was less than 10 mm/5 mm. A lip biopsy for salivary glands demonstrated foci of lymphocytic aggregations, which can be regarded as the histolopathologic features of SS.

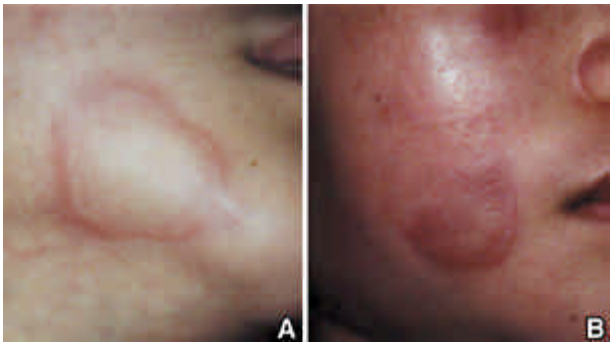

Fig. 1. Annular erythemas on the face (A: case 1, B: case 3).

The patient was diagnosed as SS/SLE. She was treated with prednisolone (20 mg/day) and hydroxychloroquine (400 mg/day). Topical corticosteroids and sunscreens were prescribed, and the use of artificial tears and gum-chewing were also advised. The AE facial lesions completely subsided in 3 weeks. Ten months later, when the disease activity of SS/SLE was in remission, several foci of recurrent AE lesions were observed on her cheeks and upper back. These lesions cleared spontaneously within a month without any treatment. At the present time, she has been feeling well with no recurrent episodes of AE after 1 year of follow-up observations.

Case 3.

A 30-year-old woman had multiple lesions of AE on the cheeks and upper arms (Fig. 1B), which occurred 3 weeks before her visit. Each erythematous lesion had spread to several centimeters in diameter. She did not feel any discomfort in the eyes and mouth. She was otherwise healthy, as determined by physical examination, and did not complain of any other systemic symptoms. Her past medical history and family history were not contributory.

She had a leukopenia (3,500-3,800/μL), hypergammaglobulinemia, and the following auto-Abs were present: ANA (titer, 1:1,260), anti-La Ab, and RF. However, tests for anti-Ro/Sm/U_1RNP revealed negative results. A biopsy specimen from the AE demonstrated perivascular and some periappendageal infiltrations of lymphocytes, with occasional neutrophils and plasma cells in the dermis. There were no epidermal changes observed. The Schirmer test result was negative. Histologic examinations of her labial salivary glands showed a mild interstitial infiltration of lymphocytes, with no foci of inflammatory cell aggregations. The patient's ultraviolet (UV) light sensitivity (determined at radiation doses of 20-50 mj/cm^2 for UVB and 20-50 J/cm^2 for UVA) was within normal limits.

The diagnosis of this patient was made as "AE with anti-La Ab" and was treated with oral prednisolone (20 mg/day) and topical corticosteroids. The AE lesions almost disappeared in 2 weeks leaving some pigmentations. During the monthly follow-up periods, the AE recurred on her upper arms after the fifth visit, and oral prednisolone was effective in suppressing the lesions over the following weeks.

RESULTS

The mean age of the patients and the age of onset of the AE was 24 years (ranging from 16 to 32 years)

Table 1. Clinical characteristics of patients with AE

Case No.	Age (year)	Sex	Lesion site	Sicca symptoms	Autoantibodies			Diagnosis
					Ro	La	RF	
1	22	F	face, upper back	+	+	+	+	SS/SLE
2	16	M	face, upper arm, palm	−	+	+	−	*
3	30	F	face, upper arm	−	−	+	+	*
4	32	M	palm, extensor knee	+	+	+	+	SS
5	20	F	face, upper arm	+	+	+	+	SS

*, AE associated with anti-Ro/La Ab

and 23.5 years (ranging from 16 to 30 years), respectively (Table 1). The interval between the disease onset and the diagnosis averaged 5 months (ranging from 2 weeks to 2 years). The follow-up periods were 6 months to up to 3 years. Among these five Korean patients, two were male and three were female. The predilection sites of the AE skin lesions appeared on the face, upper arms, and palms. Sicca symptoms were obviously present in three cases. The frequencies of positive serological findings were as follows: ANA (all 5 cases), anti-Ro and anti-La Abs (4 cases), only anti-La Ab (1 case), RF (4 cases). Other laboratory data on these patients were not significant. According to systemic reviews and objective findings made during the observation periods, the diagnosis of SS/SLE was made in one case, and primary SS was made in two cases. In the remaining two cases, the diagnosis was only "AE associated with anti-Ro/La Ab"; both patients had histories of AE for 3 weeks and 2 months, with follow-up evaluations for 10 months or so. During the follow-up periods, recurrent AE lesions were seen in three cases, however, any symptoms/signs of internal organ involvements were not identified in any of these five patients. A low to medium doses of systemic corticosteroids and/or hydroxychloroquine were effective in controlling the AE skin lesions.

DISCUSSION

In a small group of Korean patients with AE associated with anti-Ro/La Ab, subtle differences appeared among the individual cases in the serological features and in the diagnoses of the disease.

There were no apparent age and sex predominance among these five cases; however, it has been considered that AE occurs most frequently in middle-aged women with SS (2, 3, 11, 12). Clinically, the predilection sites of AE were on the face (especially, the cheeks) and upper arms, and lasted several weeks with a tendency for recurrence, as previously described among Japanese and Korean patients (1-5). The individual skin lesions did not always show up in regions exposed to the sun.

In serological examinations, four cases had anti-Ro and anti-La Abs, and one case had only anti-La Ab. In the absence of circulating anti-Ro Ab, a serological expression of anti-La Ab alone (as in case 3) is considered to be an infrequent observation in autoimmune diseases. Most reported cases of AE have anti-Ro and anti-La Abs (1-5), however, AE with anti-La Ab alone or with seronegative findings in SS, have also been reported (13, 14). There is considerable evidence that anti-Ro/La Ab plays a pathogenic role in SCLE and in neonatal LE skin diseases that have a high degree of association with anti-Ro and anti-La Abs (15, 16); consequently, we suspect that anti-Ro/La Ab may also be pathogenic in AE in SS and SS/SLE. To date, no AE-specific anti-Ro or anti-La Ab has been identified, and this may indicate that other factors are responsible for the expression of AE in this group (13, 17-19). Since there are tremendous individual variability in the expression of Ro and La antigens in the epidermal keratinocytes (19), patients with circulating anti-Ro/La Ab whose epidermal keratinocytes express greater levels of Ro/La antigens, are perhaps more susceptible to the development of AE in SS.

Among the previously reported cases of AE, the most common diagnosis was primary SS, and the next was SS/SLE (1, 3, 4, 20). Some patients did not meet the classification criteria for either SS or SLE; instead they might be cases of latent SS or latent SLE (5, 11, 12, 21, 22), as observed in the above two cases from these five patients. The differential diagnosis of these unclassified patients examined by traditional ways, lay between SS, SS/SLE, SLE, and asymptomatic clinical state; therefore it can be defined as "AE associated with anti-Ro/La Ab". In patients with AE in SS, the AE can occur as an initial or early presentation of SS before overt sicca symptoms develop (11). The author is strongly in favor of a vigilant, detectable follow-up procedure for the clinical and laboratory features of SS or SLE in unclassified cases such as seen in this study.

In the above presentation, a broad definition of the relationship between AE and anti-Ro/La Ab-positive autoimmune states was acceptable. AE in SS or SS/SLE among Orientals may be the counterpart of annular

lesions of SCLE in Caucasians. However, different pathogenic mechanisms, possibly associated with some immunogenetic variations between the two populations, may exist in the expression of annular lesions within these two racial groups.

AE associated with anti-Ro/La Ab as seen in Orientals is believed to represent a specific cutaneous manifestation of a wide spectrum of clinical states than previously recognized.

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