Localized Scleroderma is an Autoimmune Disorder

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Abstract

Objectives: There have been many studies suggesting that localized scleroderma has a strong autoimmune background, although the lesions are usually limited to the skin and subcutaneous tissue. In this review paper, we summarize the previous data on the autoimmunity of localized scleroderma mostly published in this two decades, because there has not been a review paper summarizing autoimmunity in this disorder.

Methods: We classified the previous reports into three categories: antinuclear antibodies, cytokine and soluble receptors, and cell adhesion molecules and cell surface molecules. In each category, we introduce the important investigations.

Results: High frequencies of antinuclear antibodies by the indirect immunofluorescence method using cultured cells are confirmed by many groups. Afterwards, the major autoantigen were revealed to be histones. Recently, anti-topoisomerase II alpha antibody was found to be highly frequently detected in localized scleroderma, while anti-topoisomerase I antibody which is highly specific for systemic scleroderma, was not detected in any case of localized scleroderma. Other studies related that the elevated serum cytokines and cell adhesion molecules suggested the immunoactivation of localized scleroderma.

Conclusions: Many previous studies conclude that localized scleroderma involves autoimmune abnormalities and is one of the organ-specific autoimmune disorders targeting mainly skin, although the type of autoimmune abnormalities are different from systemic sclerosis.

Introduction

Scleroderma is a chronic disease of unknown etiology characterized by skin fibrosis and is divided into two clinical entities: localized scleroderma and systemic sclerosis (SSc). Localized scleroderma differs from SSc in that it is not accompanied by Raynaud’s phenomenon, acrosclerosis and internal organ involvement and the life prognosis of patients with localized scleroderma is good.

In localized scleroderma, the lesions are usually limited to the skin and subcutaneous tissue as fatty tissue, muscle and sometimes bone beneath the cutaneous lesions, lacking Raynaud’s phenomenon, arthritis or other systemic symptoms. Tuffanelli and Winkelmann classified localized scleroderma into the following three types (1), and this classification has been widely accepted.

Morphea is usually characterized by circumscribed, sclerotic plaques with an ivory-colored center and surrounding violaceous halo. Morphea punctate is considered to be a variant of morphea, where there appear small plaque complexes.

Linear scleroderma appears in a linear bandlike distribution and scleroderma en bondes is a synonym of linear scleroderma. The frontal of frontoarietal linear scleroderma (en coup de sabre) is characterized by atrophy and a furrow or depression that extends below the level of the surrounding skin.

Generalized morphea, the most severe form of localized scleroderma, is
characterized by widespread skin involvement with multiple indurated plaques, hyperpigmentation and frequent muscle atrophy. Although the diagnostic criteria for generalized morphea differ among investigators, we defined patients as having generalized morphea when they fulfilled the following two criteria: (1) four or more lesions more than 3 cm in diameter, irrespective of whether they were of the morphea or linear type; and (2) involvement of two or more areas of the body of seven areas, the seven areas being head and neck, right upper extremity, left upper extremity, anterior trunk, posterior trunk, right lower extremity and left lower extremity (3). Patients who did not meet these criteria were diagnosed as having morphea or linear scleroderma according to the morphologic features. All of our studies were conducted using this classification.

Autoimmune abnormalities of localized scleroderma have been well recognized in the last two decades and recently this disease is generally considered to have an autoimmune background. The first description of this concept was proposed by our study in 1983, which reported high frequency of antinuclear antibodies (72.7%, 16/22), using cultured human cells as the substrate for detection by the indirect immunofluorescence method (2).

At present, the specificity of antinuclear antibodies in localized scleroderma has been revealed as described in the following sections (Table 1). In addition, an immune activation was shown in localized scleroderma suggested by the elevation of some cytokines (Table 2), soluble cell adhesion molecules and soluble cell surface antigens (Table 3).

In this literature, we summarized the previous studies related to an autoimmune background and immune activation, the latter which is comparable with diffuse form of SSc. Many previous studies conclude that localized scleroderma involves autoimmune abnormalities, though they are different from SSc.

**Antinuclear Antibody**

It was demonstrated that in an indirect immunofluorescence test for antinuclear antibody, the sensitivity varied with the type of substrate used and cultured human cell substrates had been shown to increase sensitivity compared with animal tissue sections. Therefore, cultured human cells such as HEp-2 cells are widely used for the screening test for antinuclear antibody at the clinical level nowadays.

The first investigation on the frequency of antinuclear antibody in localized scleroderma using cultured human cell substrates was reported by us in 1983 and demonstrated greater sensitivity (72.7%)(2) than animal tissue sections of previous reports (4-7). The high frequency of antinuclear antibody in localized scleroderma by an indirect immunofluorescence method using cultured cells was confirmed by other groups (8-11). Immunofluorescence staining patterns including homogeneous, speckled or nucleolar stainings were not uniform in localized scleroderma, suggesting the heterogeneity of antinuclear antibody in localized scleroderma, although a major immunofluorescence pattern was homogeneous with chromosomal staining and the major nuclear antigens of this homogeneous pattern with chromosomal staining were not identified at this time, because anti-double-stranded DNA (dsDNA) or anti-topoisomerase I antibody were not detected (2).
We have an impression that the patients with early onset have more elevated titers of antinuclear antibodies and hope to reveal that after accumulation of more cases.

**Anti-single-stranded DNA (ssDNA) antibody**

The first report on the presence of anti-single-stranded DNA antibody was by Rodnan et al. in 1977 (4), although this was an abstract and the details were not described. Seven years after this report, Falanga et al. described the high titer of anti-single-stranded DNA antibody in linear scleroderma; all seven patients were initially found to have antibodies to double-stranded DNA using the Farr technique, however, their detailed investigation using Crithidia luciliae assay and single-stranded DNA labeled with iodine 131 disclosed high titers of antibodies to single-stranded DNA and absent double-stranded DNA antibodies (12). Moreover, anti-single-stranded DNA antibody was considerably higher than the mean for unselected patients with systemic lupus erythematosus (SLE). The next year, they showed a positive correlation between anti-single-stranded DNA antibody and joint contracture or active disease with a duration of longer than 2 years (8).

We have also confirmed elevated levels of anti-single-stranded antibody in both IgG and IgM levels by ELISA analysis in localized scleroderma (13). Moreover, we found that the patients with linear scleroderma accompanied by muscle involvement such as muscle sclerosis, muscle atrophy or muscle convulsion had significantly elevated levels of anti-single-stranded DNA antibody as compared with patients without muscle involvement (14). The titer of anti-single-stranded DNA antibody is well correlated with disease activity and responds to oral corticosteroid treatment in the patients with severe muscle involvement and have shown two typical cases in the Figure 1 (unpublished data).

Subsequently, Falanga et al. reported the high frequency (59%) of anti-single-stranded DNA antibody in morphea and generalized morphea, with the highest levels of single-stranded DNA binding observed in patients with generalized morphea (14). The frequency of antibodies to single-stranded DNA was higher in patients with clinical evidence of active lesions compared with inactive disease.

Ruffatti et al. also confirmed the high frequency (38.5%) of anti-single-stranded DNA antibody by ELISA in 52 patients with localized scleroderma and found that the anti-single-stranded DNA antibodies in localized scleroderma were mainly characterized by high levels of IgM and IgA isotypes (15). In contrast, the IgG isotype of anti-single-stranded DNA antibodies significantly prevailed in SLE.

Thus, the clinical significance of anti-single-stranded DNA antibody in localized scleroderma was widely accepted, although the major nuclear antigen had still not been identified at this time, because anti-single-stranded DNA antibody does not produce any staining with the indirect immunofluorescence method of antinuclear antibody detection.

**Antihistone Antibody**

One decade after the first report on the high frequency of antinuclear antibody in
localized scleroderma (2), we found evidence suggesting the presence of antihistone antibodies in a preliminary study by the new technique of immunoblotting analysis using crude nuclear antigens. Afterwards, we confirmed the presence of antihistone antibody by ELISA and by immunoblotting analysis using purified histone antigens (16).

By ELISA, antihistone antibodies were demonstrated in 47% (23/49) of patients with localized scleroderma and in 87% (13/15) of patients with generalized morphea. Immunoblotting analysis revealed that predominant antigens were histones H1 and H3. The reactivity against H2A and H2B was also observed. The presence of antihistone antibodies correlated with that of anti-single-stranded DNA antibody.

Further studies revealed the clinical characteristics associated with antihistone antibodies in patients with localized scleroderma (3). The presence of antihistone antibodies strongly correlated with the number of morphea lesions, total number of lesions and number of involved areas of the body, however, they did not correlate with the presence or number of linear lesions. If we followed the classification definition of generalized morphea described in the introduction section, antihistone antibodies would be a good serologic marker for generalized morphea with 87% sensitivity and 74% specificity.

In addition, we determined the reactivity of antihistone antibodies with five individual histones (H1,H2A,H2B, H3 and H4) as native forms in each subgroup of localized scleroderma by ELISA. In all three groups, IgG antihistone antibodies strongly reacted with H1, H2A and H2B, and IgM antihistone antibodies strongly reacted with H1 and H2B (17). An homogeneous immunofluorescence pattern with chromosomal staining on HEp-2 cells was completely abolished by absorption with total histones, suggesting that antihistone antibodies produced homogeneous stainings by the indirect immunofluorescence technique. These data suggest that antihistone antibodies in localized scleroderma are directed against native chromatin, since H1, H2A and H2B occupy a relatively exposed component of native chromatin.

Antihistone antibodies were originally considered a highly specific serological marker of drug-induced lupus erythematous, although our studies led to the idea that antihistone antibodies are commonly detected in both SSc (18) and localized sclerderma (3, 16, 17): this concept was confirmed by other groups (10, 19).

**Rheumatoid factor**

Rheumatoid factor is generally considered to be a serological marker for rheumatoid arthritis, although the low titer of these autoantibodies was widely detected in various autoimmune disorders. In localized scleroderma, we investigated rheumatoid factor to assess the cross-reactivity of antihistone antibodies. By employing a latex agglutination test, IgM rheumatoid factor was detected in 60% of 20 patients with localized scleroderma and at a frequency of 82% in those with generalized morphea (17). In addition, an absorption test of rheumatoid factor activity with human IgG revealed no cross-reactivity of antihistone antibodies with rheumatoid factor. The high frequency of rheumatoid factor was confirmed by other investigators (9).

**Anti-topoisomerase II antibody**

Anti-topoisomerase I antibody is highly specific for diffuse cutaneous SSc (20)
and is not defected in localized scleroderma (2, 8). However, our recent study revealed that patients with localized scleroderma were frequently positive for anti-topoisomerase II α antibody (76%, 35/46), although this antibody is not completely specific for localized scleroderma; 14% (5/37) in systemic sclerosis, 8% (2/26) in SLE and 10% (2/20) in dermatomyositis (21). Immunoblotting analysis confirmed the no-cross-reactivity of anti-topoisomerase II α antibody with topoisomerase I. In addition, anti-topoisomerase II α antibody was shown to have the capability of inhibiting topoisomerase II α enzymatic activity.

Topoisomerases, which are ubiquitous enzymes, can modulate the topologic state of DNA that is critical for important biological processes such as DNA replication, nucleosome assembly and transcription. Topoisomerase I breaks and rejoins only 1 of the 2 strands for each DNA strand-passing reaction, while topoisomerase II breaks and rejoins both strands. Thus, topoisomerase family are targeting antigents both in SSc and localized scleroderma, although disease specificity is quite different. As described before, anti-topoisomerase I antibody is almost exclusively detected in SSc, whereas antitopoisomerase II α antibody was first reported in idiopathic pulmonary fibrosis (22) and various autoimmune conditions. Among them, frequency (76%) in localized scleroderma, especially that (85%, 11/13) in generalized morphea, is predominantly high.

**Antiphospholipid antibody**

Antiphospholipid antibodies are detected in a variety of autoimmune disorders, including SLE, infectious diseases, and in patients receiving drugs such as procainamide and chlopromazine. Patients with these antibodies are considered to have a higher risk of vascular thrombosis. Localized scleroderma and drug-induced lupus share many immunological characteristics. Antihistone antibodies and anti-single stranded DNA antibodies are commonly observed in both diseases, but anti-double stranded DNA antibodies were absent. Therefore we investigated whether antiphospholipid antibodies were detected in patients with localized scleroderma (23). Exceeding our expectations, IgM and/or IgG anticardiolipin antibodies were positive in 46% of patients with localized scleroderma, with 67% in generalized morphea, 35% in linear scleroderma and 30% in morphea. In generalized morphea, the frequency of IgM anticardiolipin antibody (61%) was much higher than that of IgG antibody (28%). In contrast, anti-β 2 glycoprotein I antibody was not detected in any case.

In the same study, lupus anticoagulant by screening and confirmatory coagulation tests was detected in 24% (5/21) sera from patients with localized scleroderma; all five patients had generalized morphea. Careful clinical investigation for thrombosis revealed one case with pulmonary embolism. We feel more careful observation and follow up for thrombosis should be required for patients with generalized morphea with antiphospholipid antibodies.

**Antinuclear antibodies commonly defected in SSc**

Localized scleroderma and SSc share the same main clinical features of skin sclerosis, however clinical features of both diseases are quite different and they generally considered to be two different clinical entities. In both two diseases, autoantibodies are commonly detected and immunological abnormalities involve the
pathogenesis of both diseases.

The most representative autoantibodies very frequently detected in diffuse cutaneous SSc are anti-topoisomerase I antibody and anti-RNA polymerase antibody. Anti-topoisomerase I antibody has not been detected in any study of localized scleroderma as described before (2, 8), and anti-RNA polymerase antibody has not been detected in any case of localized scleroderma either (unpublished data).

In contrast, several autoantibodies are well known to be found in limited cutaneous SSc, and the most representative autoantibody of limited cutaneous SSc is anticentromere antibody. In localized scleroderma, only one study reported 3 cases with anticentromere antibody and without evidence of Raynaud's phenomenon, acrosclerosis or visceral involvement during the follow-up period (8). However, none of other studies which screened for the presence of anticentromere antibody failed to detect this antibody (2, 3, 7, 10, 19, 20), and the cases with localized scleroderma having anticentromere antibody seem to be exceptionally rare cases in this clinical entity.

Anti-U3 RNA antibody was reported to be detected in 3 cases of 70 patients with localized scleroderma using RNA immunoprecipitation analysis (24). The presence of antibodies to Th/To RNP was also reported by the same group and being detected in 4% (3/70) patients with localized scleroderma by the same method (25). These two autoantibodies were originally identified in patients with SSc having antinucleolar antibody and were considered to be a serological marker antibody for SSc. However, these observations may explain the fact that a small number of sera from patients with localized scleroderma produced nucleolar staining by the indirect immunofluorescence method. The clinical significance of the presence of these antibodies has not been clarified at present.

**Other autoantibodies**

The previous studies show that stress proteins such as histone H2B, heart shock protein 73 (hsp-73), hsp-90 and ubiquitin may have an important role in the pathogenesis of various autoimmune diseases. As described before, histone H2B is an autoantigen in localized scleroderma, SLE and other disorders (17, 26), and histone H2B was defined as a member of the stress protein family (27). Thus, we next investigated the presence of autoantibody against hsp-73 in localized scleroderma and detected 33% (19/57). This frequency was comparable with 30% (9/30) in SLE and 41% (13/32) in SSc (28).

In addition, recent studies revealed that localized scleroderma shares the same autoantibodies with other autoimmune conditions. Anti-Fcγ receptor autoantibodies originally found in autoimmune mice (29) were detected in 54% of patients with localized scleroderma (30), the same with SSc, SLE and Sjögren syndrome (31, 32). Autoantibodies to mitochondria generally considered to be detected in primary biliary cirrhosis (PBC), were detected in 6 of 60 patients with localized scleroderma (33). These patients may comprise a unique subset of localized scleroderma designated multiple plaque type of generalized morphea with later onset, although only one patient showed laboratory abnormalities suggestive of PBC. Next, Arnett et al. reported that autoantibodies to fibrillin 1 were detected in 28% (14/50) patients with localized
scleroderma (34). Fibrillin 1 is the major component of microfibrils and Fibrillin 1 gene abnormalities are shown to be related to the animal model of scleroderma, the tight-skin mouse 1 (TSK1) (35) and the native American population with a high incidence of diffuse SSc (36). Autoantibody to fibrillin 1 is also detected in 94% of native American patients and 87% of Japanese patients with diffuse SSc and less commonly in Caucasian (34%) and African American (7%) SSc patients (37).

**Cytokines and their soluble receptors**

The autoantibody production in localized scleroderma described above can be partially attributed to abnormal T cell and/or B cell activation. Some major lymphocyte activations are mediated through circulating cytokines such as interleukin (IL)-2, IL-4 and IL-6. In our previous study, serum IL-2 levels in 27% (13/48) of patients with localized scleroderma, serum IL-4 levels in 17% (8/48) and serum IL-6 levels in 47% (23/48) were elevated, while none of the healthy controls had elevated levels of cytokines of these types (38). Moreover, activated lymphocytes express cytokine receptors on their surfaces and a soluble part of these receptors is released in proportion to state activation. We have investigated these receptors. Soluble IL-2 receptor (sIL-2R) levels have been shown to be elevated in various autoimmune disorders such as SLE and SSc (39, 40). Like the above systemic autoimmune disorders, serum levels of sIL-2R were shown to be frequently elevated (21%, 10/48), and they correlated with the number of sclerotic lesions and the number of involved areas (41). Two surface transmembrane protein receptors of IL-6 (sIL-6R), a ligand binding subunit of 80 kDa and a transducing 130 kDa glycoprotein (gp130), were known to be related to signal pathways. The soluble form of IL-6 receptor is capable of activation of the IL-6 pathway, although soluble forms of gp130 inhibit IL-6 activities through binding IL-6 receptors by activating signaling pathways. In localized scleroderma, elevated sIL-6R levels significantly correlated with the number of linear lesions and the number of body areas involved (42). Elevated sgp130 levels were also associated with the number of total lesions and the number of body areas involved.

**Soluble cell adhesion molecules**

Cell adhesion molecules are important in a variety of inflammatory and immuno-mediated mechanisms, including lymphocyte recruitment and targeting. Intracellular adhesion molecule-1 (ICAM-1: CD54), vascular cell adhesion molecule-1 (VCAM-1, CD106) and E-selection (CD62P) were expressed by activated endothelial cells. Soluble forms of these molecules are serological indicators of immune activation. In localized scleroderma, the targeting organ is limited to the circumscribed skin, although elevated levels of soluble ICAM-1 (25%, 12/48), elevated soluble VCAM-1 (19%, 11/59) and elevated soluble E-selectin (20%, 12/59) were detected (41,42).

**Soluble cell surface antigens of lymphocytes**

Several soluble cell surface antigens of lymphocytes are known as serological indicators of immune activation, as soluble CD23 (sCD23) is an indicator of B cell activation, soluble CD4 and CD8 (sCD4 and sCD8) of T cell activation, and soluble CD30 (sCD30) of Th2-type lymphocyte. All these molecules have been shown to be elevated in various autoimmune disorders and we have investigated these molecules in
localized scleroderma, where elevated frequencies of sCD23 (20%, 10/49), sCD4 (18%, 9/49), sCD8 (20%, 10/49) and sCD30 (33%, 18/55) were confirmed (43, 44, 45).

**Conclusion**

As described above, the presence of autoantibodies and the elevated serological markers suggesting immune activation show that localized scleroderma is one of the organ-specific autoimmune disorders targeting skin. Among three subsets of localized scleroderma, generalized morphea is considered to have a stronger autoimmune background than the other two types.

Whether the presence of various autoantibodies are related to the pathogenesis of cutaneous lesions remains to be determined. In addition, complicated cytokine cascades seem to be involved in the development of this disorder. Soma et al. reported the cases of localized scleroderma having multiple lesions, although they belong to Blaschko’s lines (46). We hypothesize that mutant cells derived from one cell origin distributed in the lesions belong to Blaschko’s line may be a target for the autoimmune reaction of localized scleroderma. More investigation to reveal the detailed process of the development of localized scleroderma is being conducted in our laboratory.
References


case 1

anti-SS-DNA IgG antibody

Muscle involvement

Case 1:
- Betamethasone dose:
  - 1 mg
  - 0.5 mg
  - 0.25 mg

Time:
- 0-24 month

Case 2:
- Prednisolone dose:
  - 7.5 mg
  - 5 mg
  - 2.5 mg

Time:
- 0-12 month

Skin involvement

anti-SS-DNA IgG antibody (I.U./ml)
Figure 1. Clinical courses, treatment and titers of anti-SS-DNA antibodies.

case 1. Fifteen year old female was seen with a complaint of disturbed movement of left lower leg. She was successfully treated with 1 mg of betamethasone per day.

case 2. Nine year old male was seen with a complaint of rapid increasing of multiple sclerotic plaques. He was successfully treated with 10 mg of prednisolone per day.
### Table 1  Antinuclear Antibodies in Localized Scleroderma

<table>
<thead>
<tr>
<th>Immunologic Abnormalities</th>
<th>Reference</th>
<th>Frequency in Localized Scleroderma</th>
<th>Frequency in Systemic Sclerosis</th>
<th>Frequency in Healthy Controls</th>
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<tbody>
<tr>
<td><strong>Highly specific antinuclear antibody (ANA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Homogeneous ANA by indirect immunofluorescence using HeLa cells</td>
<td>2)</td>
<td>73%</td>
<td>-</td>
<td>0%</td>
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<td>12)</td>
<td>50%</td>
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<td>-</td>
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<td>20%</td>
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<td>Frequency in Systemic Sclerosis</td>
<td>Frequency in Healthy Control</td>
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<td>s gp</td>
<td>130 43)</td>
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<td>Frequency in Systemic Sclerosis</td>
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GM: Generalized morphea  
LS: Linear Scleroderma  
M: Morphea