(60.9% vs 41.1%, $P < 0.05$). In contrast, no significant difference in the prevalence of PAH was observed between the two groups. These results suggest that young age, male sex, anti-topoisomerase I Ab positivity, severe skin sclerosis and the complication of ILD are significantly more frequent in SSc patients with DU than in SSc patients without DU.

Because severe skin sclerosis was treated with corticosteroids, the rate of treatment with corticosteroids in SSc patients with DU was higher than in the SSc patients without DU (54.2% vs 20.9%, $P < 0.01$). The patients without DU had already taken antiplatelet agents, including aspirin, sarpogrelate hydrochloride (serotonin receptor antagonist), cilostazol (phosphodiesterase inhibitor) (25.7%) and oral prostanoid, including beraprost sodium (prostaglandin I2 analog) (57.8%). The patients with DU was additionally treated with i.v. prostanoid, including lipoprostaglandin E1 (47.9%) and the endothelin receptor antagonist bosentan (25%).

There are two types of DU in SSc patients, including the digital tip type and the extensor surface type. It is considered that DU at the digital tip are caused by digital ischemia, which means impaired blood flow. On the other hand, DU at the extensor surface of the joints are predominantly caused by contracture of phalanges due to severe skin sclerosis. We summarized and compared the characteristics between digital tip type, extensor surface type and both types in Table 2. We identified 36 SSc patients with DU at the digital tip (75%), four SSc patients with DU at the extensor surface of the joints (8.3%) and eight SSc patients with DU at both locations (16.7%). Of these patients, 95.7% (22/23) with lcSSc and DU, and 94.1% (16/17) positive for anticentromere Ab with DU, had DU at the digital tip. In contrast, 91.7% (11/12) of the patients with DU at the extensor surface of the joints were dcSSc. mRTSS was higher in SSc patients with DU at the extensor surface of joints than SSc patients with DU at the digital tip (11.5 vs 17). All RNAP positive SSc patients with DU (4/4) had DU at the extensor surface of the joints. These results suggest that dcSSc type, RNAP positivity and severe skin sclerosis are more frequent in SSc patients with DU at the extensor surface of joints. These findings are consistent with the concepts that DU at the extensor surface of the joints are predominantly caused by contracture of phalanges due to severe skin sclerosis, and suggest that atherosclerosis may not be associated with DU in these patients.

**Table 2.** Demographic and clinical characteristics of SSc patients by the location of DU

| | Digital-tip ($n$ = 36) | Extensor surface of joints ($n$ = 4) | Both types ($n$ = 8) |
|---|---|---|---|
| Age (years; mean ± SE) | 61.4 ± 2.4 | 61.5 ± 1 | 54 ± 5.2 |
| mRTSS (mean ± SE) | 11.5 ± 1.4 | 17 ± 6 | 18.3 ± 3.4 |
| Sex | | | |
| Male (%) | 22.2 (8/36) | 25 (1/4) | 25 (2/8) |
| Female (%) | 77.8 (28/36) | 75 (3/4) | 75 (6/8) |
| Type | | | |
| lcSSc (%) | 61.1 (22/36) | 0 (0/4) | 12.5 (1/8) |
| dcSSc (%) | 38.9 (14/36) | 100 (4/4) | 87.5 (7/8) |
| Autoantibody | | | |
| ANA (%) | 94.4 (34/36) | 100 (4/4) | 87.5 (7/8) |
| Topo I (%) | 30.6 (11/36) | 25 (1/4) | 62.5 (5/8) |
| RNP (%) | 16.7 (6/36) | 0 (0/4) | 12.5 (1/8) |
| Centromere (%) | 44.4 (16/36) | 0 (0/4) | 12.5 (1/8) |
| RNAP (%) | 0 (0/36) | 75 (3/4) | 12.5 (1/8) |
| Complication | | | |
| ILD (%) | 47.2 (17/36) | 100 (4/4) | 87.5 (7/8) |
| PAH (%) | 8.3 (3/36) | 0 (0/4) | 12.5 (1/8) |
| Cardiac involvements (%) | 27.8 (10/36) | 25 (1/4) | 25 (2/8) |

mRTSS, modified Rodnan total skin score; lcSSc, limited cutaneous type of SSc; dcSSc, diffuse cutaneous type of SSc; ANA, antinuclear antibody; Topo I, anti-topoisomerase I antibody; RNP, anti-U1 RNP antibody; Centromere: anticentromere antibody. RNAP, anti-RNA polymerase III antibody; ILD, interstitial lung disease; PAH, pulmonary artery hypertension.

## Cardiac involvement in SSc patients with or without DU

Next, we analyzed the relationship between cardiac involvements and DU in SSc patients. It has been reported that cardiovascular complications, including valvular disease, angina and cardiac infarction, were more prevalent in SSc patients compared to healthy individuals.[16] Except for PAH, cardiac involvements, such as atrioventricular block, valvular disease, angina and cardiac infarction, were observed more frequently in SSc patients with DU compared to SSc patients without DU (27.1% vs 15%, $P < 0.05$) (Table 1). It has been recognized that serum brain natriuretic peptide (BNP) levels are high in patients with congestive heart failure, cardiac infarction and PAH.[17] Therefore, serum BNP levels in our patients were assessed. The serum BNP levels in the SSc patients (64.5 ± 7.6 pg/mL) were higher than those in the normal Japanese controls (normal, <18.4 pg/mL, indicated by dotted line in Fig. 1). However, there was no difference in serum BNP levels

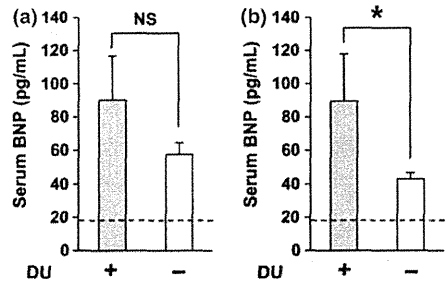


**Figure 1.** (a) Serum brain natriuretic peptide (BNP) levels in systemic sclerosis (SSc) patients with ($n$ = 41; 90.3 ± 26.3 pg/mL) or without ($n$ = 156; 57.7 ± 6.7 pg/mL) digital ulcers (DU). (b) Serum BNP levels in SSc patients with ($n$ = 38; 89.6 ± 28.2 pg/mL) or without ($n$ = 139; 43 ± 3.7 pg/mL) DU when SSc patients with pulmonary artery hypertension were excluded. Values represent mean ± standard error of the mean. *$P < 0.05$. NS, not significant. Dotted line indicates the upper limit of normal range (18.4 pg/mL).

between the two SSc groups ($DU^+$ 90.3 ± 26.3 vs $DU^-$ 57.7 ± 6.7 pg/mL) ($P = 0.22$) (Fig. 1a). Because the rate of PAH patients in SSc with or without DU was almost the same (9.3% vs 10.4%; $P = 0.825$) and these PAH patients had very high levels of serum BNP, we next analyzed the relationships between DU and BNP levels which is associated with cardiac involvements except for PAH. When SSc patients with PAH were excluded, the BNP levels in SSc patients with DU were significantly higher than those in SSc patients without DU ($DU^+$ 89.6 ± 28.2 vs $DU^-$ 43 ± 3.7 pg/mL) ($P < 0.05$) (Fig. 1b). These results indicate that DU is associated with cardiac involvements and elevated serum BNP in SSc patients.

### Extent of carotid artery atherosclerosis in SSc patients with or without DU

Atherosclerosis is the hallmark of cardiovascular diseases. In addition, patients with PAD frequently have hyperlipidemia and atherosclerosis, including carotid artery stenosis.[1] To analyze the association of hyperlipidemia with DU in SSc patients, serum cholesterol and triglycerides (TG) were compared. The levels of serum cholesterol and TG in SSc patients with or without DU were not higher than those in normal controls and were not significantly different between SSc patients with and without DU (cholesterol [mg/dL], 186.4 ± 4.7 vs 200.6 ± 3; TG [mg/dL], 137.3 ± 10.5 vs 147.4 ± 6.5). Among the SSc patients, 10.4% (5/48) of the patients with DU and 8.3% (17/206) of the patients without DU underwent treatment of hyperlipidemia ($P = 0.63$). Carotid IMT and plaques are associated with traditional risk factors for atherosclerosis and are predictors of future cardiovascular events. The mean and maximum IMT were not significantly different between the two groups (Fig. 2a). In a previous study, the maximum IMT of healthy Japanese subjects was 1.0 mm or less (indicated by a dotted line in Fig. 2a),[15] indicating that the IMT values observed in the SSc patients in this study were within the normal range. In addition, there was no significant difference in plaque score between SSc patients with and without DU (Fig. 2b). Moriwaki *et al.* classified the subjects into four groups according to plaque score: none, 0; mild, 1.1–5.0; moderate, 5.1–10.0; and severe, more than 10.0.[18] According to their criteria, the plaque scores of the SSc patients were mild, and the atherosclerotic changes were suitable for their age. These results suggest that the presence of DU in SSc is not associated with increased carotid IMT and plaques.

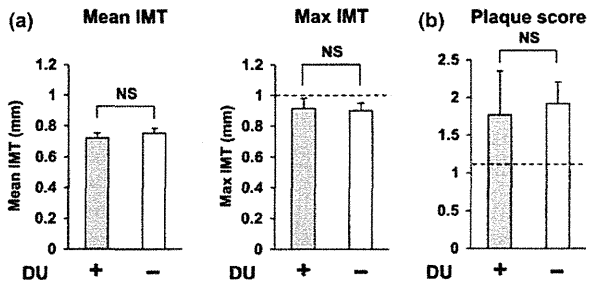


**Figure 2.** (a) Mean and maximum carotid intima-media thickness (IMT) in systemic sclerosis (SSc) patients with ($n = 21$; mean IMT, 0.72 ± 0.03 mm; maximum IMT, 0.91 ± 0.07 mm) or without ($n = 59$; mean IMT, 0.75 ± 0.03 mm; maximum IMT, 0.9 ± 0.05 mm) digital ulcers (DU). Dotted line indicates the upper limit of normal range (1.0 mm). (b) Plaque score in SSc patients with ($n = 21$; 1.77 ± 0.6) or without ($n = 59$; 1.92 ± 0.3) DU. Values represent mean ± standard error of the mean. NS, not significant. Dotted line indicates the upper limit of normal range (1.1).

## DISCUSSION

Our study identified several clinical and laboratory characteristics associated with DU in SSc patients, including male sex, young age, anti-topoisomerase I Ab positivity, severe skin sclerosis and the complication of ILD. Our findings are consistent with previous studies of SSc with DU.[19–24] The clinical and laboratory characteristics of SSc patients with DU observed in this study will help physicians to identify SSc patients at risk for developing DU, thus, allowing physicians to offer the optimal preventive and therapeutic managements for those patients. Korn *et al.* reported that bosentan may be effective in preventing new DU in SSc,[25] suggesting that bosentan might be a choice of preventive treatment of DU in SSc patients at risk for developing DU.

High BNP plasma levels predict mortality in patients with or without cardiovascular disease.[17] Patients with PAD have been reported to have higher serum BNP levels than controls.[26] Recent studies have shown that serum BNP levels are highly relevant for the diagnosis and prediction of PAH.[27] However, the association between SSc patients with DU and serum BNP levels is unknown. We found a high prevalence of cardiac involvement and elevated BNP level in SSc patients with DU, suggesting that investigating cardiac involvements and measuring BNP levels may be clinically important for SSc patients, especially in young male patients with severe skin sclerosis, anti-topoisomerase I Ab positivity and ILD.

It has been reported that SSc patients have an increased risk of atherosclerosis, including hyperlipidemia and carotid artery stenosis, compared with normal subjects.[28] However, in previous studies, the association between SSc and elevated IMT has been controversial. Nussinovitch *et al.* summarized 12 previous studies of IMT in SSc patients; five studies found that IMT was elevated in SSc patients, but seven studies found that it was not.[12] In addition, two studies reported that the number of carotid plaques was higher in SSc patients than in normal controls.[28,29] To the best of our knowledge, no previous studies analyzed the association between DU and carotid artery atherosclerosis in SSc patients. Our study did not find significant differences in serum cholesterol or TG levels, carotid IMT values plaque scores between SSc patients with and without DU, suggesting that there is no association between carotid artery atherosclerosis and DU in Japanese patients with SSc. This discrepancy may be partially explained by ethnicity or lifestyle.

The pathogenesis of DU in SSc is not clear. Endothelial dysfunction and intimal thickening of the vessel wall are thought to

be involved in the pathogenesis of DU.[19] Our results suggest that atherosclerotic changes may not be primarily involved in the development of DU in SSc; however, further investigation is warranted in patients of different ethnicities and varying lifestyles.

**CONFLICT OF INTEREST:** The authors have no conflicts of interest to declare.

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# Skin Sclerosis with Elevation of Serum Interleukin-6 That Is Possibly Associated with Immunoglobulin 4-Related Disease

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Dear Editor:

An 82-year-old Japanese man was found to have retroperitoneal fibrosis in 2006 and treated with 60 mg/day prednisolone, which tapered and finally discontinued in January 2010. Arthritis of both knees developed in 2011, and total knee arthroplasty was performed in January 2013. Histopathological examination of the joint synovium showed numerous infiltrations of plasma cells and fibrosis around the infiltrate (Fig. 1A). The ratio of immunoglobulin $G4^+$ ($IgG4^+$)/$IgG^+$ plasma cells per high-power field was >60% (Fig. 1B). Serum IgG4 was elevated (125 mg/dl; reference, 4~108 mg/dl). IgG4-related disease (IgG4-RD) with involvement of the retroperitoneum and joint synovium was established. Computed tomography showed the remaining lesion of retroperitoneal fibrosis but did not show additional lesions of IgG4-RD. One month after the operation, he noticed an indurated skin lesion in his lower leg. Physical examination revealed diffuse, indurated skin sclerosis in his left lower leg (Fig. 1C). Histological examination revealed severe fibrosis in entire dermis and infiltrations of plasma cells around blood vessels (Fig. 1D). $IgG4^+$ cells were rarely observed. Skin sclerosis appeared sequentially after the operation on the joint synovium and the establishment of the diagnosis of IgG4-RD, suggesting that skin sclerosis may be considered as the possible symptom of IgG4-RD. Topical and oral prednisolone (15 mg/day) was given. The skin sclerosis became soft gradually, and serum IgG4 levels returned to the reference range. We also found that the serum interleukin (IL)-6 level was elevated (13 pg/ml; reference, <0.5) before treatment and returned to the reference range in parallel with clinical improvement.

IgG4-RD is a newly recognized disorder characterized by the infiltration of abundant $IgG4^+$ plasma cells in lesions accompanied by fibrotic or sclerotic changes[1,2]. Skin involvement was rarely reported[1]. Ikeda et al.[1] described the skin lesions as erythematous nodules, papules, and areas of induration. They also reported that the common feature of the skin lesions was the localization near the main area of IgG4-RD involvement, and that the appearance of skin lesions after the onset of IgG4-RD range from 2 months to 3 years[1]. Of note, our case is consistent with these features.

Recently, there has been a report on 3 patients who had skin lesions with abundant infiltration of IgG4-bearing plasma cells and an elevated serum IL-6[2]. An increase in IL-6 concentration has also been reported in other plasma cell-related diseases, including multicentric Castleman's disease and cutaneous plasmacytosis[3]. IL-6 induces B-cell proliferation and terminal differentiation, immunoglobulin secretion, and an acute inflammatory-phase response, suggesting that IL-6 might be important in the pathogenesis of IgG4-RD.

Concerning IL-6 and fibrosis, it has been reported that serum IL-6 correlated with the extent of skin fibrosis in systemic sclerosis[4]. In addition, IL-6 enhanced collagen type I production from human fibroblasts in an *in vitro* assay[5],

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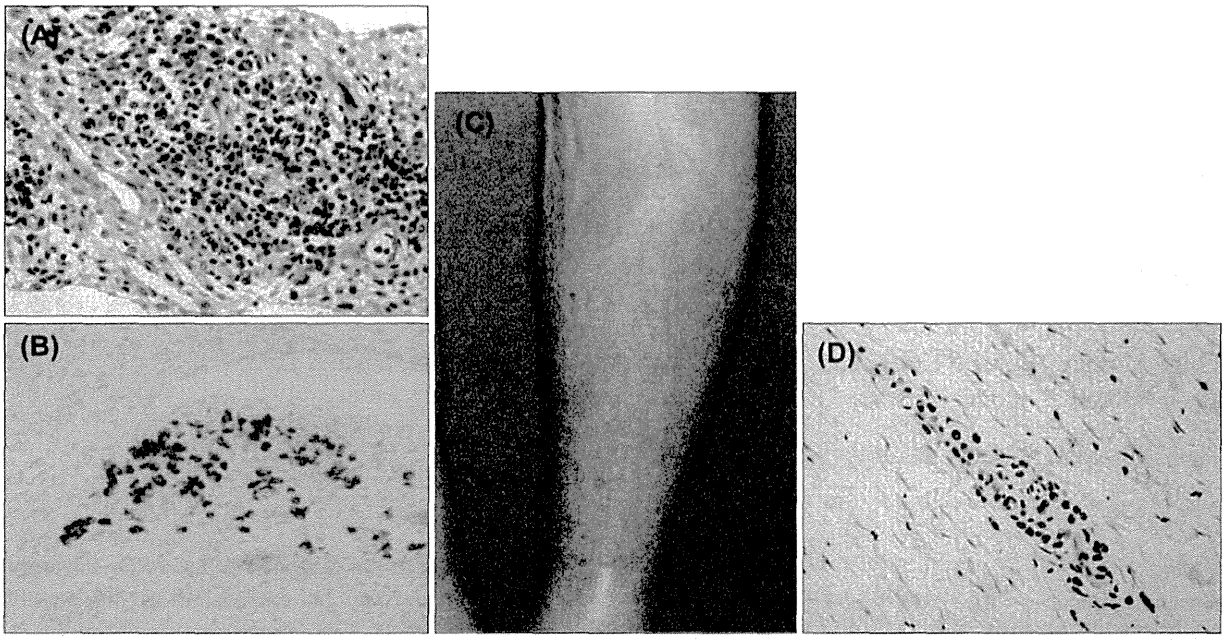


**Fig. 1.** (A) Histopathological examination of the joint synovium. Infiltration of plasma cells and fibrosis (H&E, ×400). (B) Infiltration of $IgG4^+$ plasma cells (×400). (C) Physical examination of the lower leg. Diffuse, indurated skin sclerosis in the left lower leg. (D) Histological examination of skin sclerosis. Severe fibrosis in the entire dermis and infiltrations of plasma cells around blood vessels were observed (H&E, ×400).

suggesting that IL-6 is a potent stimulator of collagen production in fibroblasts, leading to skin sclerosis. Thus, the elevation of serum IL-6 level might be associated with the pathogenesis of skin sclerosis in our case. However, further examinations on the relation between IL-6 in IgG4-RD and fibrosis are warranted.

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SHORT COMMUNICATION

# Methotrexate-induced Accelerated Nodulosis in a Patient with Rheumatoid Arthritis and Scleroderma

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Rheumatoid nodules are characterised by subcutaneous nodular lesions at pressure areas, such as finger joints and the extensor area of the forearm. Rheumatoid nodules occur in approximately 30–40% of patients with rheumatoid arthritis (RA), and usually reflect high levels of disease activity and severity of RA (1, 2). Rheumatoid nodules are often confused with methotrexate (MTX)-induced accelerated nodulosis. MTX-induced accelerated nodulosis is characterised by multiple subcutaneous nodules occurring during MTX treatment for RA, and is seen in 8% or 11.6% of MTX-treated patients (3–5). Herein, we report a case of accelerated nodulosis during MTX therapy in a patient with RA and scleroderma.

## CASE REPORT

A 68-year-old Japanese woman was diagnosed as having scleroderma, at the age of 61. The diagnosis was based on Raynaud's phenomenon, skin sclerosis of bilateral fingers and arms, the pathological findings of fibrosis of the dermis of her forearm, as well as the presence of anti-centromere antibodies. Two years later, in 2007, the diagnosis of RA was established, based on arthritis of fingers and knees, swollen joints of hands, bone erosive lesions of fingers in X-ray analysis, and positive testing for rheumatoid factor and anti-circulated citrullinated peptide antibodies. Nodules on the fingers and hands were not observed. Treatment with oral MTX 4 mg/week was started from May 2008, and the dose of MTX was increased up to 8 mg/week from April 2009. In addition, treatment with etanercept 50 mg/week was started from August 2008. Three months after increase in the dose of MTX, the disease was well controlled.

In December 2011, after 3 years of treatment with MTX and etanercept, multiple indurated dome-shaped small nodules (< 5 mm) on her fingers were noticed (Fig. 1A), and the number rapidly increased. Some of nodules were observed in the extra-articular area of fingers. Histopathological examination of a nodule was performed under the differential diagnosis of MTX induced accelerated nodulosis or rheumatoid nodules, and showed the central fibrinoid necrosis surrounded by lymphocytes and epithelioid cells in a palisade arrangement (Fig. 2). Since the disease activity of RA was well controlled, we considered that these nodules were induced by the use of MTX, and treatment with MTX was stopped in September 2012, however, etanercept was continued. Four months later, most of subcutaneous nodules had disappeared (Fig. 1B), and local recurrence has not occurred during a 6-month follow-up period. In addition, the disease activity of scleroderma was also well controlled.

## DISCUSSION

Many case reports and reviews have been published on MTX-induced accelerated nodulosis. Most reported cases occurred in patients with RA and some in patients with systemic lupus erythematosus (SLE) treated with MTX (6). To the best of our knowledge, no report has been published about MTX-induced accelerated nodulosis in a patient with RA and scleroderma.

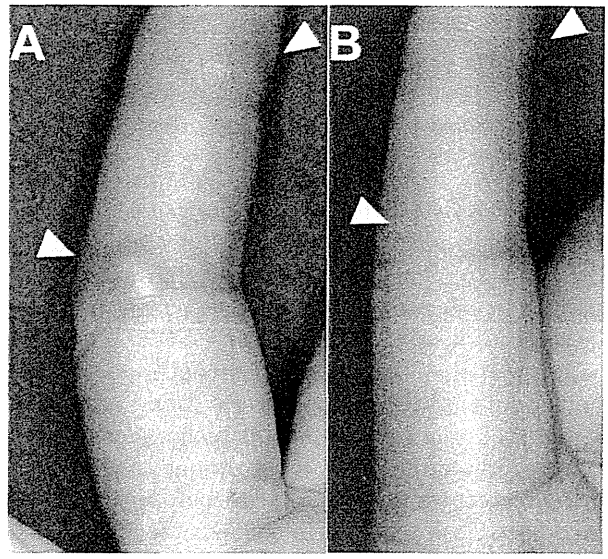


*Fig. 1.* Multiple indurated dome-shaped small nodules on fingers (A). Four months after discontinuance of methotrexate, almost all subcutaneous nodules had disappeared (B).

Kerstens et al. (3) reported that accelerated nodulosis occurred exclusively in patients receiving MTX, and the estimated incidence was 8% in a double-blind study. In addition, Berkun et al. (4) reported that overall rate of MTX-induced accelerated nodulosis was 11.6% of MTX-treated RA patients. Patatanian & Thompson (5) summarised 27 case reports of MTX-induced accelerated nodulosis, mentioning that 64% of the patients had finger involvement, and other sites were the elbows, knees and feet. In addition, they showed that the time between initiation of MTX administration and the occurrence of accelerated nodulosis was variable from 3 months to 12 years, and cumulative dose of MTX ranged from 90 to 7,200 mg. In our case, nodules were noticed 3 years after MTX administration, and the cumulative dose of MTX was approximately 1,800 mg.

It is known that the characteristic features of MTX-induced accelerated nodulosis compared with rheumatoid nodules are that MTX-induced nodules have a more rapid onset and growth, the size of nodules is smaller,

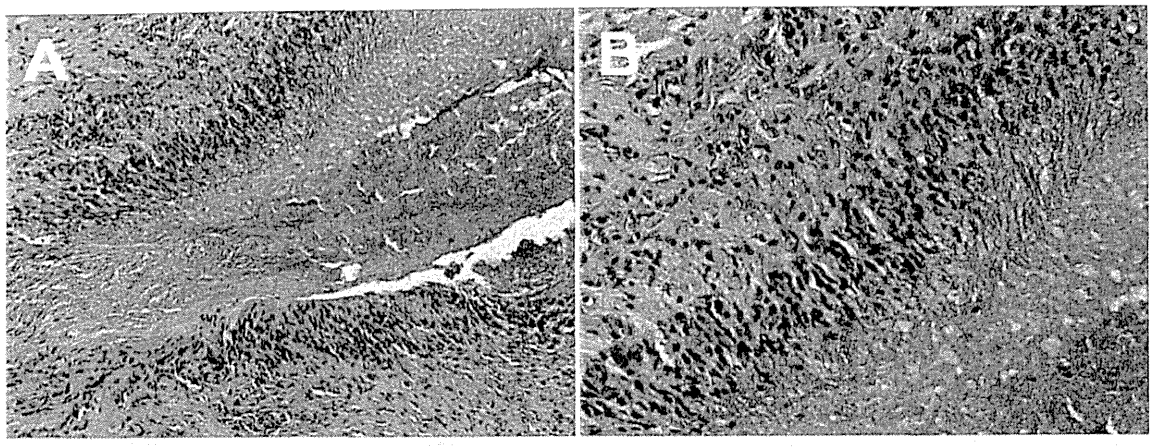


*Fig. 2.* Histopathological examination of a nodule. The central fibrinoid necrosis surrounded by lymphocytes and epithelioid cells in a palisade arrangement H&E: A: ×200, B: ×400).

and they follow a different distribution, such as on the hands, feet, and ears in comparison with around the articular area of fingers in rheumatoid nodules (3). In addition, accelerated nodulosis develops even when RA disease activity is well controlled.

Kekow et al. (7) reported etanercept-induced accelerated nodulosis in a patient with RA, and Cunnane et al. (8) reported that MTX-induced accelerated nodulosis was exacerbated by etanercept. In our case, treatment with etanercept was started 3 years before onset of accelerated nodulosis, suggesting that etanercept might have been responsible for nodulosis. However, the nodules disappeared after discontinuance of MTX even though etanercept was continued, indicating that accelerated nodulosis was induced by MTX.

The pathogenesis of MTX-induced accelerated nodulosis has not been elucidated. Merrill et al. (9) suggested that MTX induces adenosine production from infiltrating monocytes, which stimulates the adenosine A1 receptor, resulting in enhancement of giant cell formation *in vitro*. They concluded that drugs which inhibit adenosine A1 receptor might be useful for the treatment of MTX-induced accelerated nodulosis.

The primary treatment is discontinuance of MTX. However, Patatanian & Thompson (5) reported that nodules regressed by additional administration of anti-rheumatic drugs, incuding hydroxychloroquine, colchicine, sulfasalazine, azathioprine and D-penicillamine in some patients in whom MTX could not be discontinued. They suggested that physicians need to consider these treatment options when discontinuation of MTX is impossible.

Since most of MTX-induced accelerated nodulosis might be misdiagnosed as being rheumatoid nodules, MTX-induced accelerated nodulosis may not be so rare. Therefore, it is important for dermatologists and rheumatologists to make the distinction between MTX-induced accelerated nodulosis and rheumatoid nodules so an early diagnosis can be made and an appropriate treatment can be initiated.

*The authors declare no conflicts of interest.*

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ORIGINAL ARTICLE

# Demographic and clinical features of autoimmune thyroid disorder in Japanese patients with systemic sclerosis

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## ABSTRACT

**Autoimmune thyroid disorders (AITD) are characterized by the impairment of the thyroid gland as a result of systemic or organ-specific autoimmune disorders, and the presence of antithyroid autoantibodies, such as antithyroglobulin antibody (AbTg) and antithyroid peroxidase antibody (AbTPO). Several studies have reported the association of AITD with systemic sclerosis (SSc). However, none of those studies analyzed the association between AITD and skin sclerosis in SSc patients. The aim of this study was to examine the demographic and clinical features of SSc patients with AITD treated in our department. Of a total of 210 SSc patients, we identified 30 with AITD (14.3%), including 29 with Hashimoto's disease (13.8%) and one patient with Graves' disease (0.5%), indicating that hypothyroidism was more common among SSc patients with AITD. All patients with AITD were female, and anticentromere antibody positivity, the complication of Sjögren's syndrome, severe facial skin sclerosis and atrophy of the thyroid gland were significantly prevalent in SSc patients with AITD. SSc patients with such clinical features may be at high risk of AITD and require regular follow up of thyroid function including ultrasonography and the examination of serum hormone levels to start an early treatment.**

**Key words:** antithyroglobulin antibody, antithyroid peroxidase antibody, autoimmune thyroid disorders, Hashimoto's disease, hyperthyroidism (Graves' disease), systemic sclerosis.

## INTRODUCTION

Autoimmune thyroid disorders (AITD) are systemic or organ-specific autoimmune disorders characterized by the presence of antithyroid autoantibodies, such as antithyroglobulin antibody (AbTg) and antithyroid peroxidase antibody (AbTPO). It has been found that antithyroid autoantibodies can be detected in more than 30% of patients with collagen diseases such as rheumatoid arthritis,[1] systemic lupus erythematosus[2–4] and Sjögren's syndrome (SjS),[5] and that there is a high incidence of concurrent Hashimoto's disease. Systemic scleroderma (SSc) is a connective tissue disease characterized by angiopathy, fibrosis of multiple organs and immunological disorder. Several reports have pointed out the concurrence of SSc and AITD.[6–17] However, there are few reports of demographic and clinical features, including skin sclerosis and the complications, of SSc patients with AITD. In this study, we examined the characteristics of SSc with AITD in 210 patients treated in our department from 2006 to date.

## METHODS

### Patients

Two hundred and eleven SSc patients treated in our department from 2006 to date were initially included, and one patient, who had been taking amiodarone and lithium preparations that could affect thyroid function, was excluded. Therefore, 210 SSc patients were enrolled in this study. Diagnosis of SSc was established according to the criteria proposed by the American College of Rheumatology.[18] Diagnosis of limited cutaneous type SSc (lcSSc) and diffuse cutaneous type SSc was made by the classification proposed by LeRoy *et al.*[19] This study was approved by the local research ethics committee of Gunma University. Written informed consent was obtained from patients.

### Clinical and laboratory assessments

Skin sclerosis was scored using the modified Rodnan total skin score (mRTSS).[20] Interstitial lung disease (ILD) was defined as ground-glass opacity and interstitial fibrosis as observed on

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computed tomography. Pulmonary artery hypertension (PAH) was determined on the basis of elevated right ventricular systolic blood pressure (>45 mmHg) by echocardiography, and subsequently as elevated mean pulmonary artery pressure (>25 mmHg) by cardiac catheterization. SjS was diagnosed according to the Japanese criteria (1999 revised criteria, Ministry of Health, Labor and Welfare).[21]

### Autoimmune thyroid disorders

Autoimmune thyroid disorder is defined as the presence of both antithyroid autoantibodies, such as AbTg and AbTPO, and the abnormal findings of thyroid gland by ultrasonography. AITD includes hyperthyroidism (Graves' disease) and hypothyroidism (Hashimoto's disease). Graves' disease was diagnosed on the basis of clinical symptoms including goiter, tachycardia, exophthalmos, finger shivering and increased sweating, as well as hormone levels, anti-thyroid-stimulating hormones (TSH) receptor antibodies, radioactive iodine and technetium thyroid uptake rate. Hashimoto's disease was diagnosed on the basis of serological test measurements of free triiodothyronine (FT3), free thyroxine (FT4), TSH, AbTg and AbTPO, as well as thyroid ultrasonography findings. "Clinical" hypothyroidism in AITD is defined as the presence of antithyroid autoantibodies, and a condition with abnormal findings of ultrasonography with decreased serum levels of FT4 or FT3. "Subclinical" hypothyroidism in AITD is defined as the presence of antithyroid autoantibodies, and a condition with abnormal findings of ultrasonography without decreased serum levels of FT4 or FT3.

### Statistics

*P*-values were calculated using Student's *t*-test or $\chi^2$-test analysis. Error bars represent standard errors of the mean. $P < 0.05$ was considered to be statistically significant. A multiple logistic regression analysis was conducted with the presence of AITD as the dependent variable and significant variables are shown in Table 2 (sex, anti-topoisomerase I antibody [Topo I], anticentromere antibody [ACA] and SjS) as the independent variables using SPSS Statistics version 21 (IBM, Armonk, NY, USA). Antinuclear antibodies (ANA) were excluded from the independent variables because all SSc patients with AITD were positive for ANA.

## RESULTS

### Characteristics of AITD in SSc patients

Thirty SSc patients with AITD (14.3%) were identified among 210 SSc patients (Table 1). Among 30 SSc patients with AITD, 29 with hypothyroidism (Hashimoto's disease) and one with hyperthyroidism (Graves' disease) were identified, suggesting that the great majority of SSc patients with AITD had hypothyroidism.

In hypothyroidism (Hashimoto's disease), clinical hypothyroidism was defined as a clinical syndrome of hypothyroidism associated with decreased serum levels of FT4 or FT3, elevated TSH and abnormal findings of ultrasonography. Subclinical hypothyroidism was defined as a condition with abnormal findings of ultrasonography, but without decreased serum levels of FT4 or FT3. In the present study, we identified 20 clinical hypothyroidism patients (9.5%) and nine subclinical hypothyroidism patients (4.3%) (Table 1). Next, we examined the prevalence of thyroid autoantibodies (Table 1). In the 210 SSc patients overall, 28.6% (60/210) of SSc patients had either or both AbTg and AbTPO. Among these SSc patients, 50% (30/60) of patients had the abnormal ultrasonographic findings, being consistent with the diagnosis of AITD. However, 50% (30/60) of patients did not have the abnormal thyroid ultrasonographic findings, and these patients were excluded from the AITD group in this study. These results suggest that ultrasonography analysis is essential for the SSc patients with antithyroid autoantibody, AbTg and/or AbTPO to make an early diagnosis of AITD, and to start appropriate treatments.

### Comparison of demographic and clinical characteristics of SSc patients with and without AITD

Demographic and clinical characteristics of SSc patients with or without AITD are summarized in Table 2. The mean age of the SSc patients with AITD was 65.5 years and that of patients without AITD was 64.9 years. All SSc patients with AITD were female, while 87.2% of SSc patients without AITD were female ($P < 0.05$). There was a tendency that lcSSc was more prevalent in SSc patients with AITD than patients without AITD (80% vs 68.9%, $P = 0.217$).

With respect to autoantibodies, SSc patients with AITD were significantly more positive for ANA or ACA compared with SSc patients without AITD (ANA, 100% vs 88.3%, $P < 0.05$; ACA, 63.3% vs 40.0%, $P < 0.05$). In contrast, SSc patients with AITD were significantly less frequently positive for Topo I compared with SSc patients without AITD (6.7% vs 22.3%, $P < 0.05$). There was no difference in the prevalence of anti-U1 RNP

**Table 1.** Characteristics of AITD in SSc patients

| | SSc ($n = 210$) | SSc with AITD ($n = 30$) | SSc without AITD ($n = 180$) |
|---|---|---|---|
| Diagnosis | | | |
| Graves' disease (%) | 0.48 (1/210) | 3.3 (1/30) | |
| Hashimoto's disease (%) | 13.8 (29/210) | 96.7 (29/30) | |
| Clinical hypothyroidism (%) | 9.5 (20/210) | 66.7 (20/30) | |
| Subclinical hypothyroidism (%) | 4.3 (9/210) | 30.0 (9/30) | |
| Autoantibody | | | |
| AbTg (%) | 19.5 (41/210) | 66.7 (20/30) | 14.3 (21/180) |
| AbTPO (%) | 22.4 (47/210) | 73.3 (22/30) | 14.8 (25/180) |
| AbTg or AbTPO (%) | 28.6 (60/210) | 100 (30/30) | 16.7 (30/180) |

AbTg, antithyroglobulin antibody; AbTPO, antithyroid peroxidase antibody; AITD, autoimmune thyroid disorder; SSc, systemic sclerosis.

**Table 2.** Demographic and clinical characteristics of all SSc patients and SSc patients with or without AITD

| | SSc ($n$ = 210) | SSc with AITD ($n$ = 30) | SSc without AITD ($n$ = 180) | $P$ |
|---|---|---|---|---|
| Age (years, mean ± SE) | 64.9 ± 0.7 | 65.5 ± 1.6 | 64.9 ± 0.8 | 0.186 |
| Sex | | | | |
| Male (%) | 11.0 (23/210) | 0 (0/30) | 12.8 (23/180) | 0.038 |
| Female (%) | 89.0 (187/210) | 100 (30/30) | 87.2 (157/180) | |
| Type | | | | |
| lcSSc (%) | 70.5 (148/210) | 80.0 (24/30) | 68.9 (124/180) | 0.217 |
| dcSSc (%) | 29.5 (62/210) | 20.0 (6/30) | 31.1 (56/180) | |
| Autoantibody | | | | |
| ANA (%) | 90.0 (189/210) | 100 (30/30) | 88.3 (159/180) | <0.05 |
| Topo I (%) | 21.0 (44/210) | 6.7 (2/30) | 22.3 (42/180) | <0.05 |
| RNP (%) | 12.9 (27/210) | 16.7 (5/30) | 12.2 (22/180) | 0.501 |
| ACA (%) | 43.3 (91/210) | 63.3 (19/30) | 40.0 (72/180) | <0.05 |
| SS-A (%) | 26.2 (55/210) | 36.7 (11/30) | 24.4 (44/180) | 0.159 |
| SS-B (%) | 4.3 (9/210) | 3.3 (1/30) | 4.4 (8/180) | 0.781 |
| Complication | | | | |
| ILD (%) | 41.0 (86/210) | 30.0 (9/30) | 42.8 (77/180) | 0.188 |
| PAH (%) | 8.1 (17/210) | 10.0 (3/30) | 7.8 (14/180) | 0.68 |
| DU (%) | 17.1 (36/210) | 16.7 (5/30) | 17.2 (31/180) | 0.94 |
| CI (%) | 10.0 (21/210) | 13.3 (4/30) | 9.4 (17/180) | 0.511 |
| SjS (%) | 30.0 (63/210) | 50.0 (15/30) | 26.7 (48/180) | <0.01 |

ACA, anti-centromere antibody; AITD, autoimmune thyroid disorder; ANA, antinuclear antibody; CI, cardiovascular involvements; dcSSc, diffuse cutaneous type of SSc; DU, digital ulcers; ILD, interstitial lung disease; lcSSc, limited cutaneous type of SSc; PAH, pulmonary artery hypertension; RNP, anti-U1 RNP antibody; SE, standard error; SSc, systemic sclerosis; SjS, Sjögren's syndrome; Topo I, anti-topoisomerase I antibody.

antibody (RNP), and anti-SS-A and SS-B antibodies between the two groups.

There was a tendency that ILD was less prevalent in SSc patients with AITD than patients without AITD (30% vs 42.8%, $P$ = 0.188). There was no significant difference in the prevalence of digital ulcers, PAH and cardiovascular involvements. SjS was more frequent in SSc patients with AITD than SSc patients without AITD (50% vs 26.7%, $P$ < 0.01). These results indicate that hypothyroidism was more common among SSc patients with AITD, and that ANA or ACA positivity and the complication of SjS were significantly prevalent in SSc patients with AITD.

Multiple logistic regression analysis showed that the complication of SjS was significantly and positively correlated with having AITD (odds ratio [OR] = 2.39, 95% confidence interval [CI] = 1.07–5.35, $P$ = 0.034). The positivity for ACA was also selected as an independent variable, although the statistical significance was borderline (OR = 2.25, 95% CI = 0.99–5.10, $P$ = 0.052).

## Association of facial skin sclerosis and SSc patients with AITD

Next, we analyzed the extent of skin sclerosis in SSc patients with clinical AITD, subclinical AITD or without AITD. No significant difference of mRTSS was observed between the three groups (6.29 ± 2.0 vs 6.33 ± 3.8 vs 5.62 ± 0.5) (Fig. 1a). It is of note that skin score of the face in SSc patients with clinical AITD was significantly higher than those in SSc patients with subclinical AITD and without AITD (0.86 ± 0.1 vs 0.22 ± 0.2 vs 0.21 ± 0.04) (Fig. 1b). These results suggest that severe facial skin sclerosis may be associated with abnormal thyroid hormone levels in SSc patients with AITD.

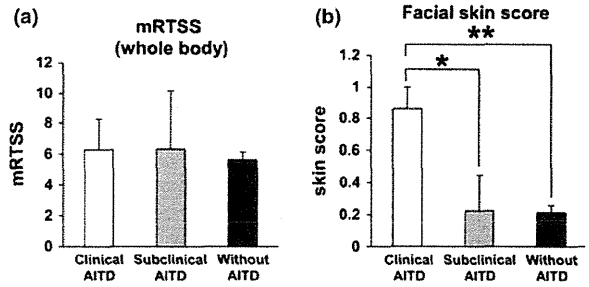


**Figure 1.** (a) Modified Rodnan total skin score (mRTSS) of whole body in SSc patients with clinical or subclinical autoimmune thyroid disorders (AITD) or without AITD. Values represent mean ± standard error of the mean. (b) Skin score of face in systemic sclerosis patients with clinical or subclinical AITD or without AITD. Values represent mean ± standard error of the mean. $^{**}P$ < 0.01; $^{*}P$ < 0.05.

## Ultrasonography findings in SSc patients with AITD

Ultrasonographic examination of thyroid gland was performed in SSc patients with auto-thyroid antibodies or the abnormal serum thyroid hormone levels. Ultrasonography findings of SSc patients with AITD revealed primarily mild swelling of glands, whereas there were few patients with swelling of 20 mL or

more (Table 3). In contrast, the atrophy of glands (<6 mL) was significantly prevalent in SSc patients with AITD (13.3% vs 0%, $P < 0.05$) (Table 3). There was no significant difference between the two groups in the prevalence of thyroid nodules or thyroid cancer. These results suggest that the atrophy of thyroid glands may be associated with AITD in SSc patients.

## DISCUSSION

In the present study, we found that the prevalence of AITD in SSc was high at 14.3% ($n = 30$), and the most common AITD was Hashimoto's disease ($n = 29$). The prevalence is significantly higher than the general prevalence of AITD, 7.2%, in Japan,[22] which suggests that patients with SSc are prone to being complicated with AITD. Demographic and clinical features of SSc complicated with AITD revealed female sex, ANA or ACA positivity, the complication of SjS, severe facial skin sclerosis and the atrophy of thyroid gland.

In Hashimoto's disease, thyroid ultrasound findings often show mild swelling, and some patients with Hashimoto's disease exhibit severe atrophic change of the thyroid gland damaged by cytotoxic autoimmunity. Our ultrasonography study revealed that the atrophy of glands was significantly prevalent in SSc patients with AITD. It had been reported that thyroid atrophy with fibrosis was observed in SSc patients.[7] Some reports implicate SSc-induced fibrosis rather than Hashimoto's disease as the cause of thyroid dysfunction.[6,7,23] There are several case reports of SSc patients with thyroid cancer,[10,14,24] however, we were unable to find any relationship between SSc and thyroid cancer in our study.

In our SSc patients, 27.6% (58/210) of SSc patients had either or both AbTg and AbTPO. It has been reported that 12.8% of healthy Japanese adults had either or both AbTg and AbTPO,[22] suggesting that the thyroid autoantibodies AbTg and AbTPO may be more prevalent in SSc patients compared with healthy individuals. In chronic thyroiditis, the frequency of AbTg is higher than that of AbTPO (97% vs 75%).[25] However, our study demonstrated that the frequency of AbTPO is higher than that of AbTg in SSc patients with AITD (77.3% vs 66.7%), and these findings are consistent with previous reports.[11–13,15–17]

**Table 3.** Ultrasonography findings of thyroid gland in all SSc patients and SSc patients with or without AITD

| | SSc ($n = 63$) | SSc with AITD ($n = 30$) | SSc without AITD ($n = 33$) | $P$ |
|---|---|---|---|---|
| Ultrasonography findings | | | | |
| Thyroid volume >20 mL (%) | 6.3 (4/63) | 6.7 (2/30) | 6.1 (2/33) | 0.922 |
| Thyroid volume <6 mL (%) | 6.3 (4/63) | 13.3 (4/30) | 0 (0/33) | <0.05 |
| Thyroid nodule (%) | 19 (12/63) | 16.7 (5/30) | 21.2 (7/33) | 0.646 |
| Thyroid cancer (%) | 1.7 (1/63) | 0 (0/30) | 3 (1/33) | 0.345 |

AITD, autoimmune thyroid disorder; SSc, systemic sclerosis.

The detection of thyroid autoantibodies leads to the detection of subclinical hypothyroidism. While the prevalence of subclinical hypothyroidism varies due to ambiguous diagnostic criteria, in the present study, we found that the prevalence was 4.3% (9/210), and that there was no difference with the prevalence in healthy Japanese adults.[22] In subclinical hypothyroidism, there is an increased risk of cardiovascular events such as angina and myocardial infarction, and therefore the Endocrine Society recommended treatment for women wanting to become pregnant.[26] In addition, it has been reported that cardiovascular events, including valvular disease, angina and cardiac infarction, were more prevalent in SSc patients compared with healthy individuals,[27,28] suggesting that subclinical hypothyroidism in SSc patients may require early treatment. However, in our study, there was no significant difference in the prevalence of cardiovascular involvements between SSc patients with clinical and subclinical hypothyroidism (15% [3/20] vs 11.1% [1/9], $P = 0.78$), indicating that the risk of cardiovascular involvements in subclinical hypothyroidism in SSc patients is not high in our study.

There has been no report showing the relationship between skin sclerosis and AITD in SSc. In the present study, SSc patients with clinical AITD exhibited high facial skin thickness scores despite no difference in overall body skin thickness scores compared with those with subclinical AITD or without AITD, suggesting that severe facial skin sclerosis may be associated with abnormal thyroid hormone levels in SSc patients. Thyroid disease, especially hypothyroidism, often causes skin swelling or edema. We believe that a major cause of facial skin sclerosis is the consequence of myxedema. This type of edema is characteristically observed in hypothyroidism and causes non-pitting edema of the face and limbs. Insufficient thyroid hormones induce the deposition of glycosaminoglycans in the interstitial space of various organs throughout the body including the skin, cardiovascular system and nervous system. Glycosaminoglycans such as hyaluronic acid and dermatan sulfate have high water-absorption properties, resulting in increased water content in the dermis and subcutaneous tissue.[29]

The prevalence of thyroid disease increases with aging. Accordingly, AITD may develop in SSc patients during follow-up periods. Moreover, AITD may lead to subacute thyroiditis, malignant lymphoma[30] and myxedema coma. Patients at high risk of AITD require regular follow up of thyroid function to receive early treatment.

**CONFLICT OF INTEREST:** The authors declare there are no conflicts of interest.

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特集 | 他科からみた膠原病診療

# 皮膚科医からみた強皮症の皮膚病変の診療*—特にdigital ulcerに対する対策について—

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**Key Words**：systemic sclerosis(SSc), digital ulcers, Raynaud's phenomenon, peripheral circulatory disturbance, treatment

## はじめに

全身性強皮症は，皮膚および内臓臓器の線維化，血管障害，免疫異常を特徴とする発症機序不明の全身性疾患である．これら3つの病態が複雑に関連し，さまざまな症状を呈する．本稿では，線維化によって生じるさまざまな皮膚病変と血管機能異常によって生じる病変(レイノー現象や指尖部皮膚潰瘍など)について診断のポイントをあげて解説する．

## 強皮症の診断・重症度の評価に重要な皮膚病変

以下に示すさまざまな皮膚症状および身体所見を見逃さずに正しく評価することによって，早期発見，早期診断が可能になり適切な治療を開始することができる．また，強皮症と鑑別を有する皮膚硬化を生じる疾患との鑑別にも有用である．

### 1．皮膚硬化

本症の最も特徴的な皮膚所見として，四肢末端から中枢に向かって左右対称性に進行する皮膚硬化があげられる．早期では手指の浮腫性腫脹がみられる(図1)．皮膚が硬化してくると光沢を帯び，皮溝，皮丘は消失し，色素沈着や色素脱失を伴う．皮膚硬化が手指に生じた状態を強指症と呼ぶ(図2)．硬化が強くなると手指の屈曲拘縮を生じる(図3)．顔面の硬化によって表情消失や仮面様顔貌を生じる．また，口周囲の硬化によって開口障害もみられる．舌小帯においても硬化性変化が生じて舌小帯の白色化と短縮がみられる．

本症は，皮膚硬化が手指，手背や前腕にとどまるlimited cutaneous type(lcSSc)と肘を超えて及ぶdiffuse cutaneous type(dcSSc)に分類される．一般にdcSScはlcSScに比べて，内臓病変も高度で予後不良である．

皮膚硬化の評価方法としてmodified Rodnan total skin thickness score(MRSS)が用いられている．皮膚の硬化度を0～3の4段階で評価する．皮膚を両拇指ではさみ「変化なし」0，「やや厚ぼったく感じる」1，「下床との可動性を欠く」3，1と3の中間を2とする．手指ではMP関節とPIP関節の間の皮膚で行う．身体の17か所(両側の手指・手背・前腕・上腕・大腿・下腿・足趾，顔面，胸部，腹部)で評価して合計スコアを算出する．20以上は重症例と考えられる．スコアが20以上のdcSScは，20未満に比べてその後の4年間の死亡と腎クリーゼの発症が多いという報告[1]や，早期のdcSScにおいてスコア変化率が

* Medical examination of skin lesions in systemic sclerosis by dermatologists ; especially regarding the countermeasure for digital ulcers.

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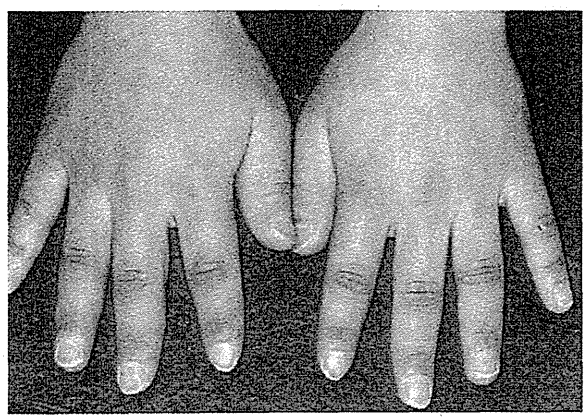

図1　指の浮腫性腫脹(早期病変)

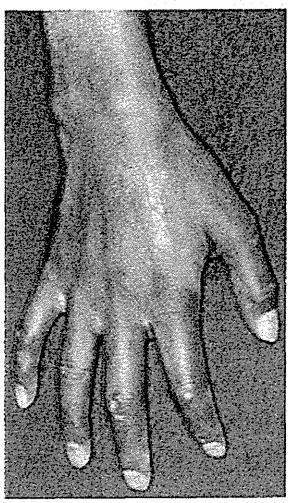

図2　強指症

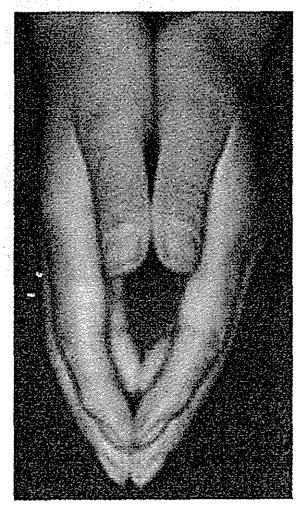

図3　手指屈曲拘縮

大きい症例では腎クリーゼと心筋病変による心不全のリスクが高く，生命予後も不良という報告[2]もあり，MRSSを継続して測定し，病勢をきちんと評価することが重要である．

2．レイノー現象

強皮症の約半数ではレイノー現象を初発症状とし，ほとんどの症例で経過中にレイノー現象を伴う．レイノー現象は，手指の小動脈の攣縮(一過性収縮)が起こり，末端部が一過性に虚血になり，その後，再還流が起こることによって，手指の色調が発作的に変化する現象である(図4)．寒冷刺激や精神的ストレスによって誘導される．典型的には手指の小動脈の虚血再還流によって，白(虚血)，紫(チアノーゼ)，赤(再還流)の3相性の色調に変化するが，白～紫や白～赤といった2相性もみられる．レイノー現象出現時には疼痛，痺れをきたすために患者の日常生活に著しい影響を及ぼし，極度のQOLの低下をもたらす．

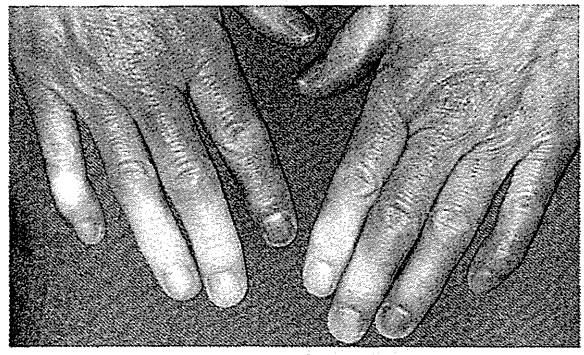

図4　レイノー現象

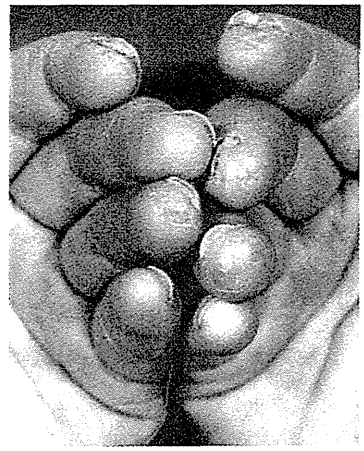

図5　指尖部の陥凹性瘢痕

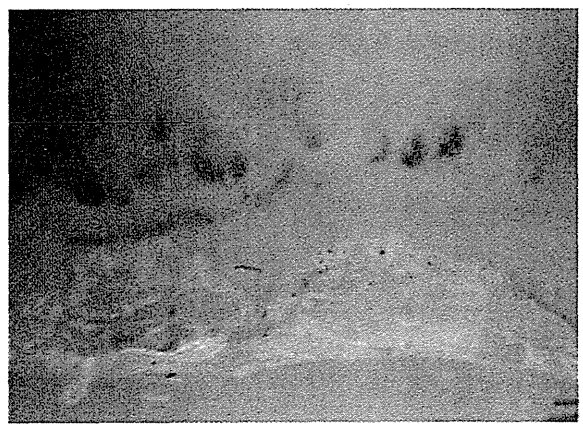

図6　後爪郭部毛細血管の拡張・蛇行や爪上皮出血点

3．指尖部陥凹性瘢痕(digital pitting scar)(図5)

米国リウマチ学会の診断基準にも含まれている所見であり，疾患特異性が高い．必ずしも皮膚潰瘍が先行するわけではない．

4．爪部毛細血管の変化

自覚症状に乏しいため見逃されがちであるが，capillaroscopyやdermoscopyを用いて拡大す

図7　爪上皮出血点，爪上皮延長

ると後爪郭部毛細血管の異常が詳細に観察できる．後爪郭部毛細血管の拡張・蛇行や爪上皮の出血〔爪上皮出血点：nail fold bleeding(NFB)〕(図6, 7)がみられる．これらの所見が3指以上に観察された場合は疾患特異性が高い．また，爪上皮の延長を伴っていることが多い(図7)．これらの所見は早期から観察されるため，早期診断に重要な所見である．

5．指尖部皮膚潰瘍(digital ulcer)(図8)

手指や足趾は，皮膚線維化や末梢血流低下による循環障害をきたしやすく，軽微な外傷によって皮膚潰瘍を生じる．強皮症に伴う指尖部皮膚潰瘍は難治例が多く，細菌感染を起こした場合には，潰瘍が拡大し骨髄炎や関節炎を伴い，指趾切断に至る可能性もある．また，創部の細菌感染から敗血症を呈し，生命予後を左右することもあるため早期の適切な治療が重要である．

強皮症に伴う末梢循環不全の原因として，一過性の血管の攣縮(レイノー現象)によるものと，慢性の血管機能障害によるものが考えられる．慢性の血管機能障害は，血管平滑筋の増殖や細胞外基質の線維化による血管内腔の狭小化や，骨髄由来の血管内皮前駆細胞の減少，機能異常による血管新生能低下などによって生じると考えられている[3)4)]．

われわれは当科における指尖部皮膚潰瘍を生じた強皮症の臨床的特徴，心疾患や脂質異常，動脈硬化との関連性について検討した[5)]．2006年から現在までに当科通院加療中の全身性強皮症患者(254例)を対象に，指尖部皮膚潰瘍を生じた症例(45例)について検討した．指尖部皮膚潰瘍を伴う全身性強皮症患者は，潰瘍のない強皮症患者と比べて，男性の割合が高い，dcSScが多い，皮膚硬化が強い，抗トポイソメラーゼI抗体陽性例が多いという特徴がみられた．また，間質性肺炎合併例が多くみられるという特徴もみられた．これらの結果は，欧米で行われたいくつかの同様の研究結果と一致していた[6)~9)]．また，心病変との関連性についても検討したところ，指尖部皮膚潰瘍を伴う強皮症では，肺高血圧症以外の心疾患を有する症例が多く，BNP値が高かった．これらの指尖部皮膚潰瘍を生じやすい強皮症患者の特徴は，発症予防や早期治療の介入に応用できる．

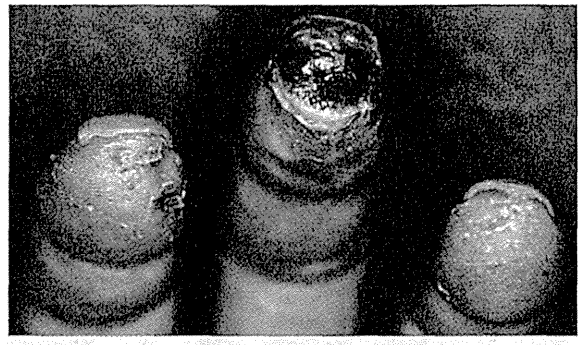

図8　指尖部皮膚潰瘍

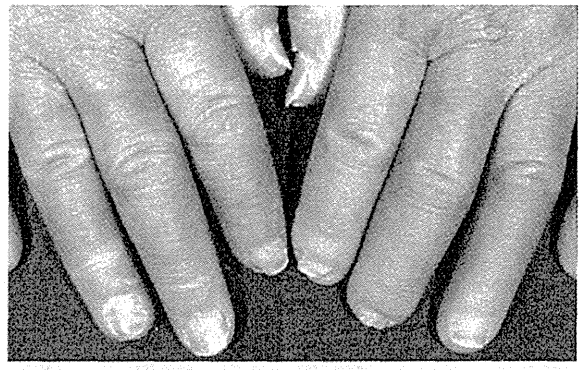

図9　指末節骨短縮

さらに指尖部潰瘍を生じた強皮症患者における脂質異常症や頸動脈エコーを用いた頸動脈病変の程度について検討を行った．指尖部皮膚潰瘍の有無で患者群を分けて比較したが，脂質異常症，頸動脈病変(動脈硬化，狭窄)といったアテローム性動脈硬化との関連性はみられなかった．また，強皮症患者でアテローム性動脈硬化のリスクが高いということもなかった．したがって，強

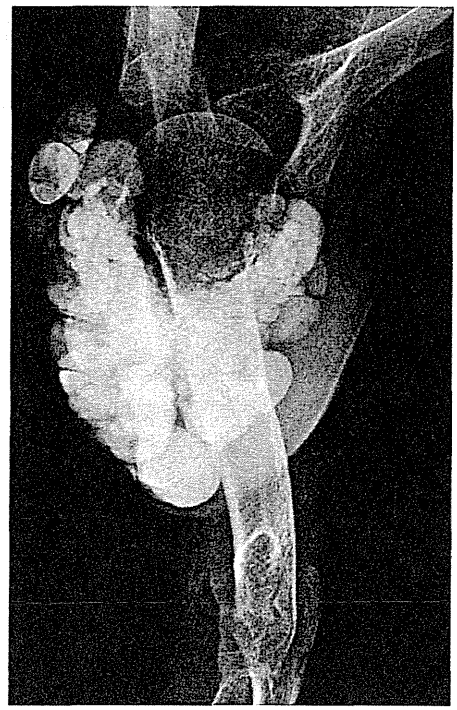

図10　皮下多発石灰化(肩関節周囲)

皮症の指尖部皮膚潰瘍はアテローム性動脈硬化以外の原因による循環障害によって発症することが示唆された.

6. その他

毛細血管拡張, 指末節骨短縮(図9), 皮下石灰沈着(図10)[10]などがみられる.

## 鑑別診断

1. 関節リウマチ

手指の浮腫性腫脹と関節腫脹がみられ(図11), 全身性強皮症の早期病変との鑑別を要する. MRIによる関節滑膜炎の評価が鑑別に有用である.

2. 好酸球性筋膜炎

手指の硬化を欠き, 四肢の浮腫性硬化として発症する. 運動に続発することが多く, 急激に発症する. オレンジ皮状皮膚(orange peel sign), 血管に沿った皮膚の陥凹(groove sign)(図12)がみられる. 末梢血好酸球増多を伴う例が多い.

3. POEMS症候群(Crow-Fukase syndrome)

皮膚病変として, 強皮症様の皮膚硬化, レイノー現象, 色素沈着がみられ, 全身性強皮症との鑑別を要する. 多発血管腫, 多毛を生じる. M蛋白血症, 内分泌異常, 神経炎を伴う.

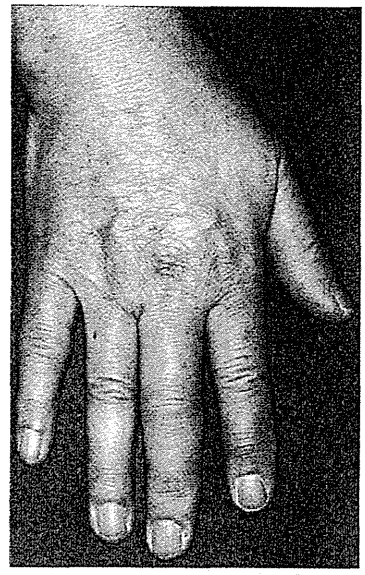

図11　関節リウマチ：手指の浮腫性腫脹と関節腫脹

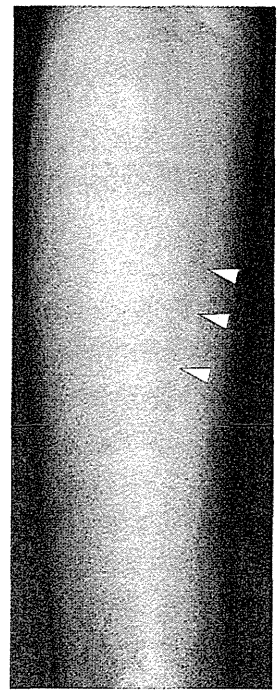

図12　好酸球性筋膜炎
血管に沿った皮膚の陥凹(groove sign)あり.

4. Werner症候群

遺伝性の早老症である. 四肢末端の皮膚萎縮, 硬化(図13)がみられ, 強皮症との鑑別を要する. 特有の顔貌, 白髪, 白内障, 高度の動脈硬化などによって鑑別できる.

5. 糖尿病性強指症(diabetic sclerodactyly)

糖尿病患者の手指にみられる皮膚硬化, 拘縮は強皮症との鑑別を要する. 137人の糖尿病患者

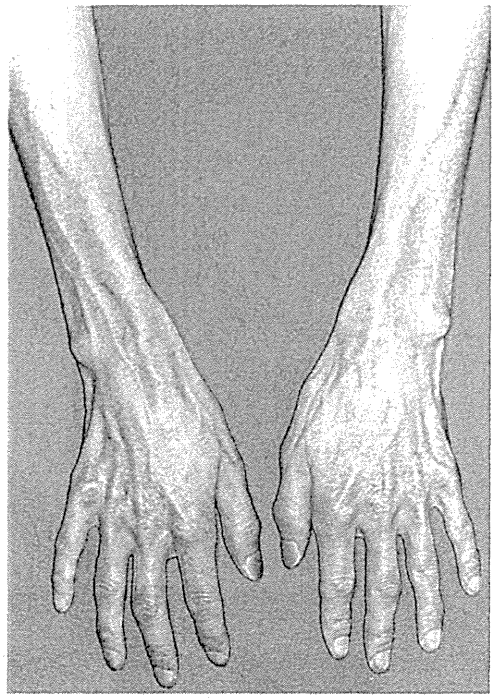

図13　Werner症候群：四肢末端の皮膚萎縮，硬化

のうち47人(34％)に手指硬化が，26人(19％)に手指節間関節の中程度の拘縮がみられるとの報告がある[11]．

6．限局性強皮症

限局性の皮膚硬化(図14)で，内臓病変を欠く．ときには筋や骨に硬化性変化を生じる．本症が全身性強皮症に合併することもあり注意を要する[12]．

7．レイノー病

レイノー現象は，明らかな原因のない一次性レイノー現象(レイノー病)と，基礎疾患を有する二次性レイノー現象に分類される．レイノー現象を生じる基礎疾患として，膠原病〔強皮症，全身性エリテマトーデス，混合性結合組織病(MCTD)など〕や動脈閉塞性疾患などさまざまな

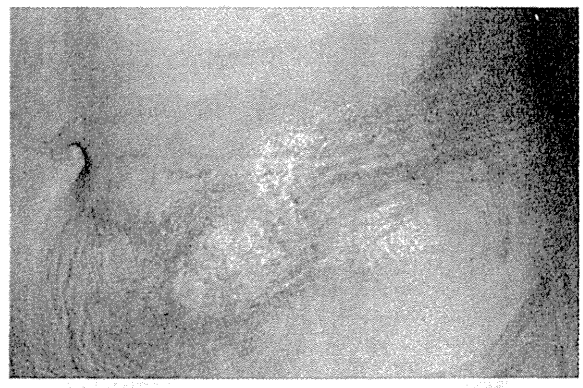

図14　限局性強皮症

要因があるため，これらを除外する必要がある．

## 治　療

1．皮膚硬化の治療

急速に皮膚硬化が進行する場合や，浮腫性硬化が主体の早期病変，皮膚硬化の出現から6年以内のdcSScに対してはステロイド治療の適応となる．PSL 20～30 mg/dayの初期量より開始する．スキンスコア30以上の重症例にはパルス療法も考慮する．早期にステロイド治療を行うことによって，急速な病変の進行を抑えることができるため，皮膚硬化がまだ肘を超えていないがしばらくすると全身に皮膚硬化が及ぶ可能性のあるdcSScの早期例を判断することが重要となる．表1にdcSScの早期例の特徴を示す[13]．このなかで注目すべきは抗RNAポリメラーゼIII抗体陽性例である．特徴として，皮膚硬化が強く，急速に進行することや，腎クリーゼの発症リスクが高いこと，悪性腫瘍の合併が多いことがあげられる[14]．そのほか，シクロホスファミドやメソトレキサートなどの免疫抑制剤が使用される．また，紫外線治療(UVA，NB-

表1　dcSScの早期例の特徴

| | |
|---|---|
| 皮膚硬化の進行 | 急速に進行 |
| 皮膚の状態 | 浮腫，光沢，色素沈着を伴うことが多い |
| レイノー現象と皮膚硬化 | 出現がほぼ同時(ときにレイノーを欠如) |
| 関節屈曲拘縮 | 高率に伴う |
| 腱摩擦音 | 高率に伴う |
| 爪部毛細血管所見 | ループ拡張と軽度の血管減少 |
| 臓器障害 | 腎クリーゼ，心筋障害 |
| 自己抗体 | 抗トポイソメラーゼI抗体，抗RNAポリメラーゼIII抗体 |

(文献[13]より引用)

UVB）も行われている．

2．指尖部循環障害（レイノー現象，指尖部潰瘍）の治療

まず，治療の一環として生活習慣の改善は非常に重要であり，寒冷曝露を避けること，保温を心がけること，そして禁煙を指導することが重要である．手袋や靴下，携帯用カイロの使用を勧める．

強皮症のレイノー現象や指尖部末梢循環障害に対する治療としては，一般的にはビタミンE製剤（ニコチン酸トコフェロールなど），カルシウム拮抗薬（ニフェジピンなど），プロスタグランジン製剤（内服；リマプロスト，ベラプロスト，注射；アルプロスタジル），セロトニン拮抗薬（塩酸サルポグレラート），血小板凝集抑制薬（シロスタゾール，ジピリダモール）などの血管拡張作用，抗血小板作用のある薬剤を使用する[15]．抗凝固薬のアルガトロバンの点滴も有用である[16][17]．

以下にそれぞれの薬剤の作用機序と有効報告例の詳細を示す．

（1）カルシウム拮抗薬

カルシウム拮抗薬（ニフェジピン）はレイノー現象の頻度，期間，重症度を有意に軽減させることがランダム化コントロール試験によって示されており[18]，カルシウム拮抗薬はレイノー現象に有用と考えられる．しかし，皮膚潰瘍に対する検討はされておらず不明である．

（2）プロスタグランジン製剤

プロスタグランジン製剤の経口薬としては，プロスタグランジン$E_1$（$PGE_1$）のリマプロスト（オパルモン®），$PGI_2$のベラプロスト（ドルナー®，プロサイリン®）などが用いられる．また，注射薬として，$PGE_1$製剤のアルプロスタジル（プロスタンディン®）やリポ$PGE_1$製剤（リプル®，パルクス®）が用いられ，血管拡張作用や血小板凝集抑制作用によってレイノー現象や皮膚潰瘍を改善させると考えられる．また，リポ$PGE_1$製剤は強皮症患者において，静注後に血中の可溶性intercellular adhesion molecule-1（ICAM-1）や可溶性L-セレクチンの濃度を低下させることが報告されており，これらの機序を介した末梢循環障害の改善も推測されている[19][20]．

（3）抗血小板薬

〔シロスタゾール（プレタール®）〕

Phosphodiesterase（ホスホジエステラーゼ）阻害剤であり，血小板凝集抑制作用と血管平滑筋の増殖や収縮を抑制する作用を有する．シロスタゾール内服によって強皮症に伴うレイノー現象の症状が改善したことが報告されている[21]．

レイノー現象を有する強皮症患者ではセロトニンの血中濃度が高いことや，血小板から放出されるセロトニンの血管平滑筋収縮作用や血小板凝集作用が病態に関与することが示唆されている．抗セロトニン作用をもつ塩酸サルポグレラート（アンプラーグ®）が強皮症患者においてレイノー現象の改善に有効であったとする報告がある[22]．

（4）エンドセリン受容体拮抗薬（ボセンタン）

エンドセリンは主に血管内皮細胞より産生される分泌蛋白質であり，血管平滑筋細胞や血管周皮細胞（ペリサイト）上に発現するエンドセリン受容体に結合して強力な血管収縮作用や細胞増殖促進作用を示す．

強皮症患者血清中のエンドセリン濃度は，正常人より高値であることが知られており，エンドセリンが強皮症の病態形成に関与することが示唆される．強皮症に伴う肺高血圧症においては，エンドセリンによる肺動脈の血管収縮や血管平滑筋細胞に対する増殖促進作用がその病態に大きく関与している．エンドセリン受容体（A型とB型）拮抗薬であるボセンタンは，エンドセリン受容体とエンドセリンとの結合を阻害し，その作用を抑制することによって肺高血圧症の進行を抑制し，予後を改善する[23]．

近年，指尖部循環障害やレイノー現象に対してもボセンタンが奏効した症例が国内外から数多く報告されている．強皮症に伴うレイノー現象と続発する指尖部潰瘍に対するボセンタンの効果を検討したところ，ボセンタンの内服によって皮膚潰瘍の新生が有意に抑制されることが多施設二重盲検試験で示されている[24]～[26]．また，われわれも，強皮症による難治性指尖潰瘍に対してボセンタンを使用し，その有用性を確認している[27]．これらの報告より，ボセンタンは強皮症による難治性指尖潰瘍の新たな治療法として期待

されるが，現在のところ，本邦ではWHO機能分類でIII度以上の肺高血圧症にしか保険適応はない．肝障害など重篤な副作用が生じることもあり，使用に際しては慎重なモニタリングの必要がある．また，A型エンドセリン受容体拮抗薬であるアンブリセンタンもその効果が期待される．

(5) ホスホジエステラーゼ5阻害剤（シルデナフィル，タダラフィル）

ホスホジエステラーゼ5阻害剤は，血管平滑筋細胞を介した血管拡張作用を有するcGMPの分解を抑制することによって血管拡張作用を促す．ホスホジエステラーゼ5阻害剤であるシルデナフィルやタダラフィルもWHO機能分類II度以上の肺高血圧症の治療薬として本邦でも保険適応がある．シルデナフィルやタダラフィルが他剤に抵抗性のレイノー現象の頻度を抑制し，重症度も改善したとする報告がある[28]．強皮症による難治性指尖部皮膚潰瘍の治癒を促すことも期待される．

(6) スタチン

レイノー現象を伴う強皮症患者84人に対して無作為試験を行い，スタチン（アトルバスタチン）の効果を検討した結果，指尖部潰瘍の頻度と疼痛を軽減することが報告されているが，今後のさらなる検討が必要である[29]．

## 局所治療について

手指の皮膚潰瘍に対する外用治療は，褥瘡の処置に準じて，壊死の除去作用を有するゲーベンクリーム®，肉芽増生，再上皮化作用を有するトラフェルミン噴霧薬（フィブラストスプレー®），プロスタンディン軟膏®，オルセノン軟膏®，アクトシン軟膏®などを使用して適切な処置を行う．

われわれは，強皮症に伴う手指の循環障害に対してニトログリセリン含有テープ貼付による治療効果を検討し，有用な効果が得られたことを報告している[30]．また，ニトログリセリン含有テープ貼付は，レイノー現象に対しても治療効果が得られている．さらに，米国ではニトログリセリン含有外用薬（MQX-503）が開発され，臨床試験（ランダム化二重盲検試験）においてレイノー現象に対して良好な結果を得ており，今後の使用が期待されている．

## その他の治療法について

その他の治療法としては，胸部交感神経切除術がレイノー現象に対して奏効した症例が報告されているが，術後敗血症などの合併症が報告されており推奨されない．交感神経ブロックも強皮症の循環障害に有効であったという報告がみられ，選択肢の1つとなるかもしれない．血管再建術を行った例もみられるが確実な効果は得られていない．また，強皮症の難治性指尖部潰瘍に対して高圧酸素療法が奏効した症例も報告されており，有用な治療法と考えられる．近年，A型ボツリヌス毒素がレイノー現象や指尖部循環障害の治療法としても試みられ，良好な結果が報告されている[31]．

## 疼痛管理について

持続する強い疼痛は精神的なストレスを生じ，レイノー現象や血管収縮によるさらなる末梢循環障害をひき起こすと考えられるため，疼痛管理が末梢循環障害の治療には重要である．また，壊死を付す潰瘍を呈している場合，疼痛によって十分なデブリードマンを行えないことも創傷治癒の遷延化をきたす．疼痛に対する治療法としては，非ステロイド性抗炎症薬やリン酸コデインの内服，局所へのキシロカインゼリーの塗布，神経ブロックが行われている．

## ま と め

強皮症に伴うさまざまな皮膚病変は，皮膚の線維化や血管機能異常による循環障害を基盤として，寒冷や精神的ストレスなどさまざまな要因が関与する複雑な病態である．したがって，皮膚硬化の範囲，程度を正確に評価し，さらにその他の皮膚病変も詳細に観察して総合的に診断し重症度を判定することが重要である．特に，手指や足趾は皮膚硬化や血管異常による末梢循環障害症状を呈しやすい部位であるため詳細に観察し，レイノー現象や爪部毛細血管異常がみられる場合は，皮膚硬化が明確でなくても常に本症を念頭において診察，検索をする必要がある．強皮症に伴う末梢循環障害・指尖部皮膚潰瘍についてはいまだ詳細な機序は明らかになっていない．今

後，病態の解明が進み，新たな治療薬の開発につながることが期待される．

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