博士學位論文

국소성 경피증 및 전신성 경피증 양 질환에 관한 고찰 (대한민국 단일센터 연구)

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국소성 경피증 및 전신성 경피증 양 질환에 관한 고찰

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Localized Scleroderma and Scleroderma-like disorder: A Clinical Study in Korea

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Abstract

Objective: Systemic sclerosis is a rare connective tissue disorder characterized by skin fibrosis, obliterative vasculopathy and distinct autoimmune abnormalities. However, many other clinical conditions present with substantial skin fibrosis and may be confused with systemic sclerosis, leading to a misdiagnosis. Localized scleroderma (morphea) is a rare skin-limited autoimmune disease characterized by cutaneous fibrosing and obstructive vasculopathy. This disease may invade into subcutaneous fat layer and provoke permanent functional disability. Scleroderma-like disorder presents with substantial skin fibrosis and may be confused with systemic sclerosis, sometimes leading to an incorrect diagnosis. Because of its rarity, there have been few clinical surveys of patients with localized scleroderma and scleroderma-like disorders in Korea. The aim of this study was to elucidate the clinical presentation, serological data, and clinical outcomes of localized scleroderma and scleroderma-like disorder.

Methods: The clinical survey was retrospectively performed through the available medical records during a 7-year-period from 2004 to 2010, in 43 cases with localized scleroderma and 4 cases with scleroderma-like disorder.

Results: Localized scleroderma occurred primarily in females (female to male ratio being 2.6:1). Most patients were between 10 to 29 years of age. The mean age at diagnosis was 26.2 years. Plaque (51.2%) and linear morphea (37.2%) were most common. No case was associated with systemic sclerosis. The most common site of plaque morphea was trunk (47.8%). In linear type, the most commonly occurring lesions were head-neck (52.9%). The FANA was positive in 23.3% of all cases. Treatment included systemic corticosteroid, colchicine, anti-malarial agents, D-penicillamine or intralesional triamcinolone injection. Clinical improvement, including both significant and partial remission, was demonstrated in only 62.8% of the treated cases. Additionally, we experienced 4 cases of scleroderma-like disorder which did not correspond to criteria of other scleroderma.

Conclusion: Localized scleroderma is a chronic inflammatory skin-limited disease without potential risk of evolving into systemic sclerosis. In order to exclude other diseases, thorough

investigation including a history-taking, physical examination, serologic studies, and histopathologic examinations should be conducted.

Key words: Localized scleroderma, Morphea, scleroderma-like disorder, Systemic sclerosis

Introduction

The scleroderma spectrum disorders can be subdivided into three groups: systemic sclerosis, localized scleroderma, and scleroderma-like conditions, comprising a heterogeneous group of diseases linked by the presence of thickened, sclerotic skin lesions[1]. However, other manifestations of these conditions are quite diverse. These differences have required the development of differential diagnosis that takes into account the different potential complications, prognoses, and management strategies for patients with these disorders.

Systemic sclerosis is a multisystem disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs. The diagnosis of systemic sclerosis should be suspected in patients with skin thickening, puffy or swollen fingers, hand stiffness, and/or painful distal finger ulcers. Symptoms of Raynaud phenomenon and gastroesophageal reflux are often present[2].

Localized scleroderma, also known as morphea, is a rare fibrosing disorder of the skin and underlying tissues. Localized scleroderma is differentiated from systemic sclerosis based on the absence of sclerodactyly, Raynaud phenomenon, and nailfold capillary changes[1, 2]. The outcome for most patients with localized scleroderma depends upon the type and extent of the lesion. The major problem in untreated patients is not mortality, but morbidity as a result of skin, muscle, and bone atrophy. Superficial patches of localized scleroderma may be relatively benign. But localized scleroderma with deep soft tissue involvement could result in functional disabilities and cosmetic problems[3]. The underlying pathogenesis of localized scleroderma is incompletely understood at this time because of its rarity. Two possible contributing pathogenic processes include abnormal fibroblast function and autoimmune dysfunction, ultimately resulting in an imbalance of collagen production and destruction[1, 2].

The forms of localized scleroderma are classified based on clinical presentation. The most widely used classification divides localized scleroderma into five types: circumscribed morphea; linear morphea; generalized morphea; pansclerotic morphea; mixed variant morphea[4].

Scleroderma-like disorders can present diagnostic difficulties since not infrequently they imitate systemic sclerosis to such an extent that the diagnosis is quite arbitrary. The etiology of most scleroderma-like disorders is unknown, however, some have been linked to environmental, drug, or dietary exposures or metabolic abnormalities. The scleroderma-like disorders are rarely associated with sclrerodactyly or Raynaud phenomenon and serum autoantibodies do not occur[5].

There has been an increase in incidence of localized scleroderma[6]. However, only a few clinical surveys of patients with localized scleroderma have been reported in Korea. The aim of this study was to elucidate the clinical presentation, serological data, and clinical outcomes of localized scleroderma. Additionally, we include four cases of scleroderma-like disorder mimicking systemic sclerosis at the initial assessment.

Patients and methods

We performed a retrospective analysis using medical records at Jeju National University Hospital. In total 43 patients with localized scleroderma, defined by clinical and pathological findings between January 2004 and December 2010, were included in this study.

These cases satisfied the pathological findings of localized scleroderma from early to late stage of pathological findings. In the early stages of localized scleroderma, a perivascular infiltrate of predominantly lymphocytes with admixed rare plasma cells and eosinophils is seen in the reticular dermis. Endothelial cells may appear swollen, and the collagen bundles may exhibit thickening. In the late stages of localized scleroderma, the inflammatory infiltrate disappears. The collagen bundles of the reticular dermis are prominently eosinophilic, thickened, and crowding in on each other. The eccrine glands become atrophic as the hypertrophied collagen surrounds them, and there is a noticeable dearth of blood vessels. The subcutaneous fat appears “trapped” in the

dermis because of the extension of collagen into the subcutaneous tissues[6].

Medical records were reviewed for baseline demographic data, clinical characteristics including lesion size, site, laboratory data, treatment, and response to treatment.

Additionally, we reviewed the clinical presentation, serological data, and histopathologic analysis of the four cases of scleroderma-like disorder.

Results

43 cases of localized scleroderma

During the period from January 2004 to December 2010, a total of 43 patients with localized scleroderma visited Jeju National University Hospital. One patient visited in 2004, 2 in 2005, 3 in 2006, 6 in 2007, 8 in 2008, 11 in 2009, 13 in 2010 visited. Over time, the number of patients with localized scleroderma increased.

Demographics

There were 31 females (72.1%), and 12 males (27.9%); the female-to-male ratio was 2.6:1.

Age distribution ranged from under 10 to 60s at disease onset. However, age distribution of the majority of patients was between 10-29; 30.2% at 10-19, 34.9% at 20-29 (Table 1). The

mean age of the patients was 26.2 years. The mean time between the first manifestation of the disease and diagnosis was 21.2 months (range 2-36 months).

Clinical subtypes

We used the Mayo Clinic classification criteria [4]. This classification gathers the varieties of localized scleroderma into five groups: plaque morphea; generalized morphea; bullous morphea; linear scleroderma; deep morphea.

Forty-three patients were diagnosed as having localized scleroderma, 23 (51.2%) plaque morphea (Figure 1, 2), 17 (37.2%) linear scleroderma (Figure 3), 2 (4.6%) deep morphea and 1 (2.3%) generalized morphea (Figure 4). Among patients with plaque morphea, 1 patient presented with guttate morphea on the posterior trunk. Among patients with linear scleroderma, 1 patient presented with Parry-Romberg syndrome. There was no patient with bullous type morphea (Table 2).

Twenty-three patients were in the group of plaque morphea, while 11 (47.8%) presented lesions on the trunk, 7 (30.4%) presented lesions on the limbs, 5 (22.7%) presented lesions on the head-neck. Seventeen patients with linear scleroderma, 9 (52.9%) presented lesions on the head-neck, 5 (29.4%) presented lesions on the limbs, 3 (17.6%) presented lesions on the trunk. Two patients with deep morphea presented with lesions on the abdomen and limbs, while 1 generalized morphea patient presented with diffuse lesions on the trunk and limbs(Table 3).

Laboratory data

Tests were conducted for fluorescent antinuclear antibody test(FANA), anti-centromere antibody, anti-scleroderma 70 antibody(anti-Scl70 Ab), anti-polymyositis/scleroderma antibody(anti-PM/Scl Ab), anti-U1 ribo-nucleoprotein antibody(anti-U1RNP Ab), rheumatoid factor, peripheral blood immunoblobulin G(IgG) level, peripheral complete blood count with differential. FANA was positive in 10 (23.3%) patients and high titer of FANA (≥ 1:160) was found in only 2 (4.6%) patients. Among these 10 patients, those with plaque morphea were present in 5 (50%) of the cases, linear scleroderma in 3 (30%), generalized morphea in 1 (10%) and deep morphea in 1 (10%). They all presented with the speckled pattern of deposition

of FANA. Anti-centromere Ab was positive in 1 patient with generalized morphea, rheumatoid factor was positive in 1 patient with plaque morphea, and false positive of (VDRL) test was observed in 1 patient with plaque morphea. Positive anti-Scl70 Ab, anti-PM-Scl Ab, elevated IgG level was not reported. Leukopenia (WBC<4000/μL) was found in 2 (4.6%) patients, peripheral blood eosinophilia (eosinophil≥500/μL) was found in 3 (7%) patients and there was no patients with anemia.

Treatment and Response

Intralesional injection of triamcinolone was the most common choice of treatment (25.6%), followed by oral prednisolone in combination with colchicines (18.8%), oral prednisolone in combination with hydroxychloroquine (16.3%), oral prednisolone alone (11.6%), oral prednisolone in combination with D-penicillamine (9.3%). After 1 year of treatment, we observed change in clinical features of lesion (dyspigmentation, induration, erythema). Significant remission, improvement of more than 50% of the surface area, was observed in 5 (11.6%) patients (3 in intralesional injection of triamcinolone group, 1 in oral prednisolone in combination with hydroxychloroquine, 1 in topical steroid group). Partial remission, improvement of less than 50% of the surface area, was observed in 22 (51.2%) patients. However, during the course of the treatment, 16 (37.2%) patients

showed no improvement of lesions (Table 4).

4 cases of scleroderma-like disorder

We observed 4 cases of scleroderma-like disorder diagnosed with clinical, laboratory, and pathological features. The clinical findings were summarized in Table 5 and laboratory and histopathological findings were summarized in Table 6.

In Case 1, a 19-year old male with disease onset of 10 years previously, the skin lesion was nearly involving the whole torso and extremities (Figure 5). However he did not have sclerodatily, Raynaud's phenomenon, periungual telangiectasia. He had high titer of ANA (1:640) but no other specific auto-antibodies. In the histopathology, dermal collagen was increased and presented a homogenous pattern as in other cases. Collagen deposition and inflammation was found in perivascular area. However obliterative vessel change was not found (Figure 6). The range of motion of knees and ankles was limited and his clinical outcome was stationary. There were no systemic symptoms or preceding medical illness.

In Case 2, a 49-year old female was diagnosed with an unusual fibrosing disorder masquerading as systemic sclerosis. The

fibrotic induration on face, trunk and lower limbs started 2 months prior to presentation and the histopatholgy revealed collagen deposition in dermis with intact vessels as like Case 1. She had Raynaud's phenomenon and sclerodactily but did not have any abnormal finding of nail fold capillary scopy. Additionaly, she had no autoantibodies such as ANA, AHA, anti-Scl-70 Ab. She complained of shoulder and back myalgia and had xeropthalmia, acrocyanosis, and carpal tunnel syndrome. She was treated with predisolone, nifedipine, methotrexate, and D-penicillamine but the skin lesion was progressing slowly.

In Case 3, a 62 year-old male presented with symmetric induration of lower limbs and foot accompanied by severe limitation of motion in knees and ankles(Figure 7). Skin sclerosis had appeared 3 weeks previously. In histopathological finding, dermal and subcutaneous septal fibrosing was found but perivascular infiltration was not(Figure 8). He had preceding medical illness including alcoholic liver disease, chronic pancreatitis, protein loosing enteropathy, diabetic mellitus, and hypertension. His finding was very similar to scleredema adultorum of Buschke but the site of involvement was not typical. Patient's skin sclerosis and joint contracture dramatically improved after high dose steroid theraphy.

In Case 4, a 72 year-old female presented with fibrotic induration which had appeared at face, neck, back, and shoulder (Figure 9). It had started 2 years previously. Skin lesion did not correspond to scleredema in consideration of histopathologic results, but was strongly suspicious of typical scleredema adultorum of Buschke at initial presentation. Her histopathological findings were very similar to Case 3 (Figure 10). She had diabetes mellitus and cerebrovascular disease, and was treated with hydroxychloroquine, D-penicillamine, colchicines, prednisolone and the disease progress was stabilized.

Discussion

Localized scleroderma is a rare autoimmune connective tissue disease characterized by skin and underlying tissue fibrosing and obstructive vasculopathy. Patient with localized scleroderma may have systemic symptoms such as arthralgia, malaise, fatigue, as well as positive autoantibody serologies. However, the lesion of localized scleroderma is limited to those tissues derived from the mesoderm[1, 2]. Epidemiologic studies have reported incidence as 0.4 to 2.7 per 100,000 people[4, 6, 9]. Like many other connective tissue diseases, a female predominance of 2.4 to 4.2:1 has been reported[3, 6, 11] and our study concurs with this observation.

Plaque morphea makes up the vast majority of adult diagnoses and linear morphea is the most common variant in children. Additionally, the plaque morphea presents predominantly on the trunk[3, 4, 9-10, 12]. In our study, 10 children were included and the remainder were adults. The most common type of localized scleroderma was plaque morphea (51.2%), and 47.8% of patients with plaque morphea presented lesions on the trunk.

The diagnosis of localized scleroderma is not dependent on

laboratory testing. However, autoantibodies are a frequent finding in patients with localized scleroderma[13, 14]. FANA have been reported in 20 to 76 percent of patients with localized scleroderma[3, 13, 15-17]. In contrast, antibodies to double-stranded DNA (ds-DNA), Scl-70, centromere and topoisomerase are rarely found[3, 17]. In our study, FANA was found to be positive in 23.3% of patients. This is comparable with the prevalence previously reported. Whether these antibodies are markers that reflect the immunological component of the disease process or can have a prognostic significance is unclear. In this study, there was no correlation between these antibodies and the disease course.

Therapy for localized scleroderma has been challenging, as no established guidelines have been published. According to recently reported studies, methotrexate combined with systemic corticosteroids and ultraviolet A1(UVA1) have the most convincing data supporting their use in aggressive cases such as patients with extensive involvement, facial involvement, or involvement across joints[18-21]. For patients with limited involvement, treatment with topical tacrolimus is supported by a randomized placebo controlled trial[22]. Decisions for management must be based on extent of disease, localization, concern about possible complications, and, particularly with respect to systemic therapy, the standard of care at the time of disease diagnosis. Left untreated, the natural history for each individual plaque is to slowly soften over a period of 3 to 5 years. Many patients

experience long stretches of disease quiescence[6, 11]. As for treatment, we used low dose systemic corticosteroid, colchicines, anti-malarial agents, D-penicillamine or intralesional triamcinolone injection. However, significant clinical improvement was found in only 11.6% of the treated cases. We did not used methotrexate because there was no aggressive localized scleroderma patient in our study.

Although systemic sclerosis and scleroderma-like disorder linked with skin fibrosing, the causative factors and pathogenesis of systemic sclerosis and scleroderma-like disorders differ considerably[5]. In contrast to systemic sclerosis, the scleroderma-like disorders generally carry a good prognosis and are often self-limited[24]. It is extremely necessary to distinguish between systemic sclerosis and scleroderma-like disorders when considering therapy and prognosis.

There were no cases associated with or progressed to systemic sclerosis during the course of treatment. Undue anxiety often is created by the family's confusion of skin limited fibrotic disease and progressive systemic sclerosis. Explanation of the difference between these conditions and their expected outcome should be emphasized to the patients and their family. Additionally, the prevention of overtreatment of localized scleroderma and scleroderma-like disorder is important.

Unfortunately, our study is a retrospective observational study and has a limited scale of patients. However, this study hopefully will become a resource for future clinical research of localized scleroderma and scleroderma-like disorder.

Conclusions

We performed a retrospective observational study for localized scleroderma and scleroderma-like disorder in Korea. In total 43 patients of localized scleroderma and 4 patients of scleroderma-like disorder were included and their characteristics, laboratory data, treatment, response of treatment were analyzed. Localized scleroderma and scleroderma-like disorder had no potential risk of evolving into systemic sclerosis. Thorough investigations could be critical for diagnosis and treatment of localized scleroderma and scleroderma-like disorder.

Table 1. Age distribution of the patients with localized scleroderma

Age(years)	No.(%)
<10	3(7%)
10~19	13(30.2%)
20~29	15(34.9%)
30~39	5(11.6%)
40~49	3(7%)
50~59	2(4.7%)
60<	2(4.7%)
Total	43(100%)

Table 2. Clinical subtypes of localized scleroderma

Clinical subtypes	No.(%)
Plaque Morphea	23(51.2%)
Linear Morphea	17(37.2%)
Deep Morphea (subcutaneous type)	2(4.6%)
Generalized type	1(2.3%)
Bullous type	-
Accompanied or evolving into systemic scleroderma(systemic sclerosis)	-
Total	43(100%)

Table 3. Distribution of lesional sites in the patients with localized scleroderma

Site	No.(%)			
	Plaque Morphea	Linear Morphea	Deep Morphea	Generalized Morphea
Head & neck	5 (21.7%)	9 (52.9%)	-	-
Scalp	1	3	-	-
Face	3	6	-	-
Neck	1	0	-	-
Trunk	11 (47.8%)	3 (17.6%)	1 (50%)	1 (100%)
Chest	3	1	-	
Abdomen	3	1	1	1
Back	3	1	-	
Buttock	2	0	-	
Extremities	7 (30.4%)	5 (29.4%)	1 (50%)	-
Upper	3	2	1	-
Lower	4	3	-	-
Total	23	17	2	1

Table 4. Therapeutic modalities & clinical outcomes in localized scleroderma

Modalities	No. (%)	Outcomes(over 1 year)		
		*Significant remission	**Partial remission	No improvement
Triamcinolone intralesional injection(only)	11 (25.6%)	3	6	2
Oral prednisolone+ colchicine	8 (18.6%)	-	3	5
Oral prednisolone+ hydroxychloroquine	7 (16.3%)	1	3	3
Oral prednisolone	5 (11.6%)	-	3	2
D-penicillamine+ oral prednisolone	4 (9.3%)	-	3	1
D-penicillamine	3 (7.0%)	-	1	2
Topical corticosteroid(only)	2 (4.6%)	1	1	-
Narrow band UVB therapy(only)	1 (2.3%)	-	1	-
Topical calcipotriol(only)	1 (2.3%)	-	1	0
Topical pimecrolimus or tacrolimus(only)	1 (2.3%)	-	-	1
Total	43	5 (11.6%)	22 (51.2%)	16 (37.2%)

*Significant remission: improvement of induration and discoloration in more than 50% of lesional areas after 1 year

**Partial remission: improvement of induration and discoloration in less than 50% of lesional areas after 1 year

Table 5. Clinical findings of a case series with scleroderma-like disorder

	Case 1	Case 2	Case 3	Case 4
Age/Sex	19/M	49/F	62/M	72/F
Skin lesions				
Findings	Fibrotic induration Atrophy Poikiloderma	Fibrotic induration	Fibrotic induration	Fibrotic induration
Distribution	Upper limbs Lower limbs Torso Neck Foot dorsum	Face Trunk Lower limbs	Lower limbs Foot	Face Neck Back Shoulder
Onset	10 years	2 months	3 weeks	2 years
Raynaud phenomenon	-	+	-	-
Sclerodactyly	-	+	-	-
Nail fold abnormalities	-	-	-	-
Musculoskeletal involvement	Limitation of range of motion of knees and ankles	Shoulderache Backache	Limitation of range of motion of knees and ankles	Lower backache Shoulderache
Accompanied systemic symptoms	-	Xerophthalmia Acrocyanosis	Diarrhea Malnutrition Poorer oral intake	-
Preceding medical illness	-	Carpal tunnel syndrome	Alcoholic liver disease Chronic pancreatitis Protein losing enteropathy Diabetes mellitus Hypertension	Diabetes mellitus Cerebrovascular disease
Clinical outcome	Stationary	Slow progression	Improved	Stationary
Treatment	No	Prednisolone Nifedipine Methotrexate D-penicillamine	Prednisolone	Hydroxychloroquine D-penicillamine Colchicine Prednisolone

Table 6. Laboratory and histopathologic findings of a case series with scleroderma-like disorder

	Case 1	Case 2	Case 3	Case 4
ANA	(1:640)	-	-	-
Anti-Scl-70 Ab	-	-	-	-
Anti-centromere Ab	-	-	-	-
Leukopenia	-	-	-	-
Anemia	-	-	-	-
Eosinophilia	+	-	-	-
Histopathologic findings				
Epidermal changes	-	-	-	-
Increased collagenosis (dermal fibrosis)	+	+	+	+
Subcutaneous septal fibrosing	+	+	+	+
Perivascular and/or periadnexal inflammation	+	+	-	-
Adnexal atropy or abnormal ascending into upper dermis	+	+	-	-
Vascular changes	+	+	-	-
Collagenal homogenization	+	+	-	-
Mucin deposition	-	-	-	-
Amyloid depotion	-	-	-	-

*Vascular changes: endothelial hyperplasia, capillary dilatation, vascular luminal obstruction

* Mucin deposition: alcian blue, PAS, D-PAS, mucicarmine, colloidal iron

* Amyloid depotion: alkaline Congo red

Fig. 1. Plaque type localized scleroderma(localized morphea) involving left forearm in a 12-year-old male.

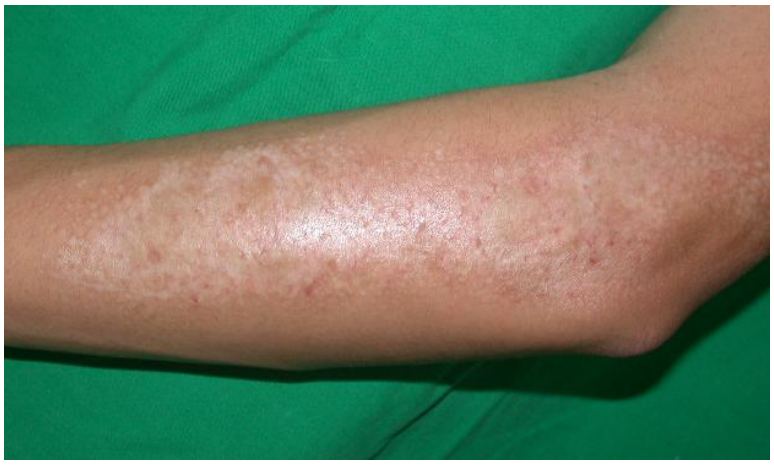


Fig. 2. Plaque type localized scleroderma(localized morphea) involving perioral zones in a 16-year-old female patient

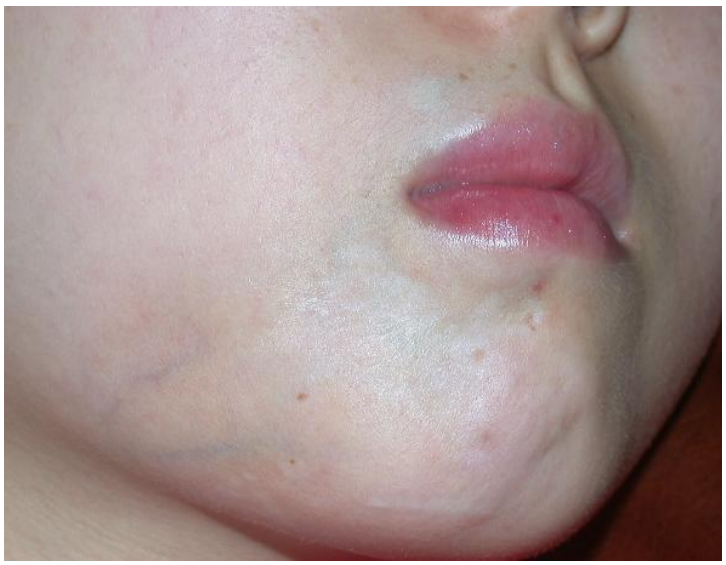


Fig. 3. Linear type localized scleroderma(linear morphea) occurring in the left flank region of a 25-year-old female patient

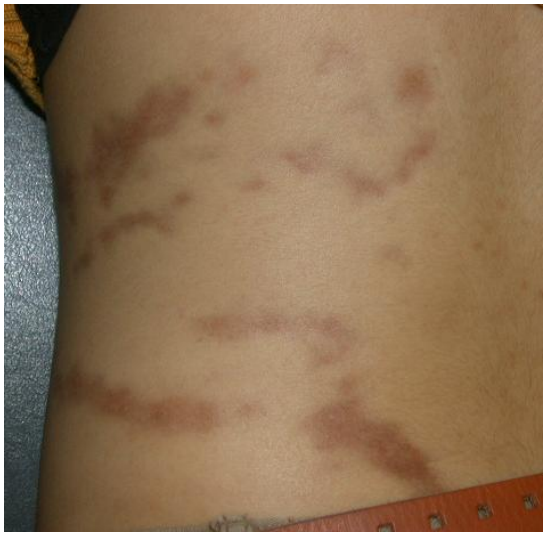


Fig. 4. Generalized scleroderma(pansclerotic morphea) invading full torso in a 19-year-old male patient.

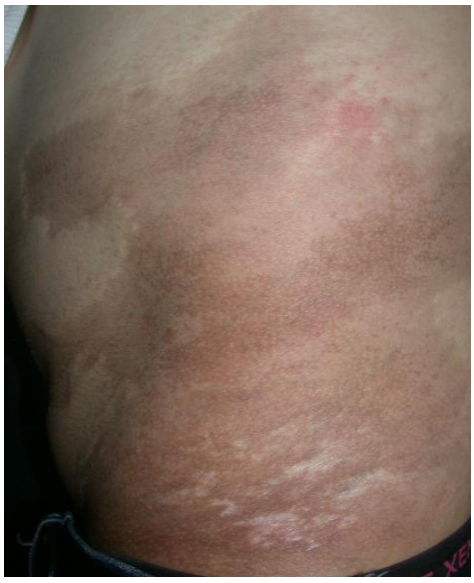


Fig. 5. Hyperpigmented fibrotic induration and poikilodermic surface changes of right forearm (Case 1).

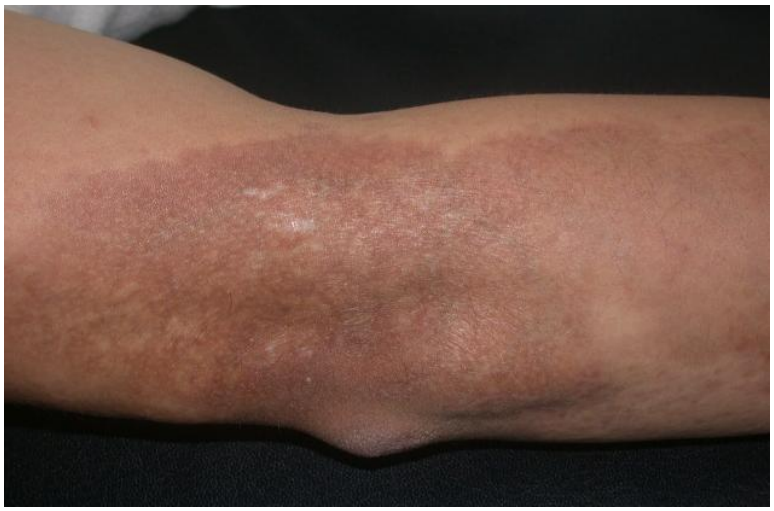


Fig. 6. Increased thickened collagen fibers in the reticular dermis with sparse inflammatory cellular perivascular infiltrates (H&E, ×100, Case 1).

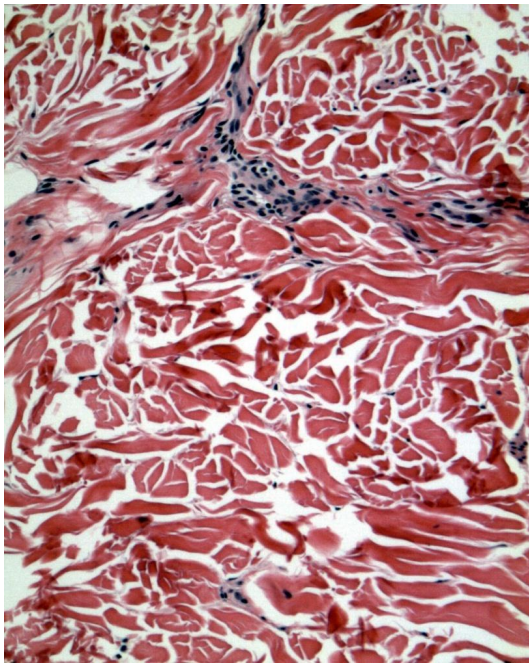


Fig. 7. Sclerotic skin change of lower extremities including both ankles (Case 3).

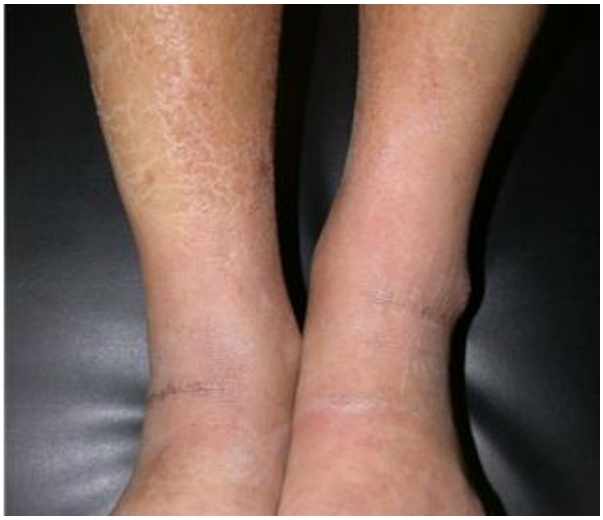


Fig. 8. Dermal and subcutaneous septal fibrosing without perivascular infiltration (Case 3).

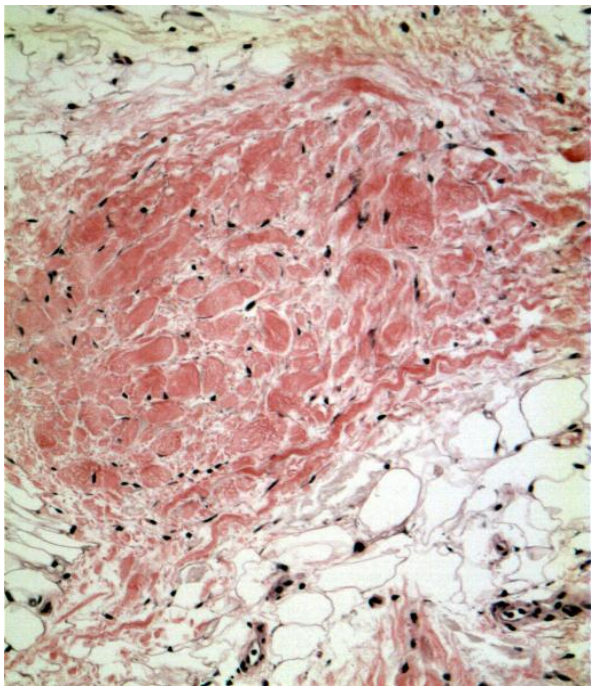


Fig. 9. Ill-delimited, faint red hued, fibrotic induration of upper torso and shoulder (Case 4).

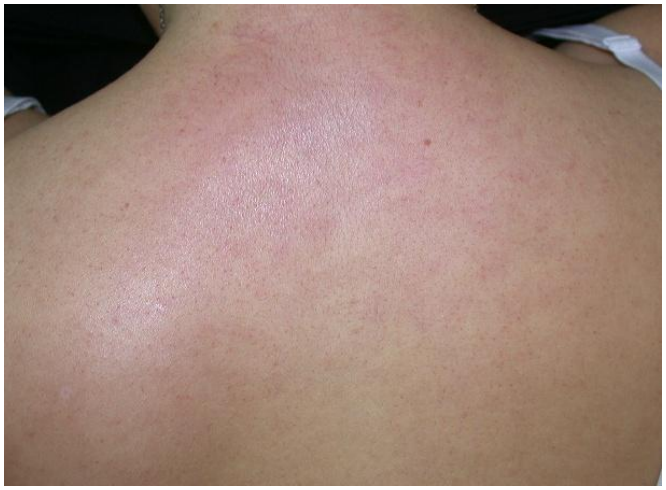
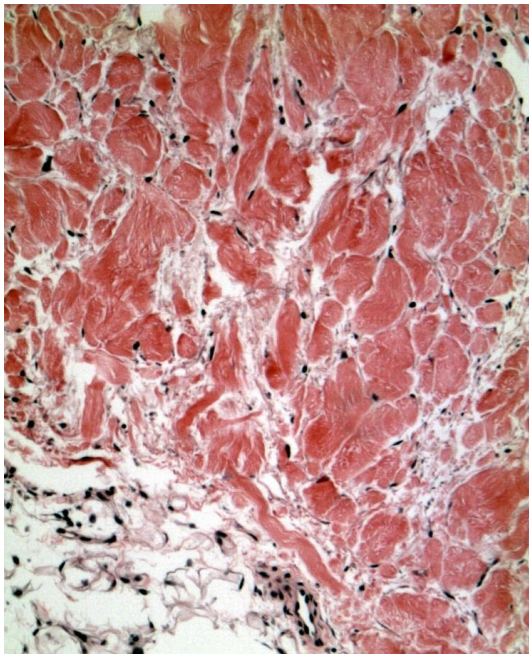


Fig. 10. Increased newly producing individual collagen fibers replacing subcutaneous fat septum (H&E, ×200, Case 4).



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