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The Effect of Traditional Korean Medicine Treatment on CREST Syndrome: A Case Report

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ABSTRACT

CREST syndrome is a form of limited cutaneous scleroderma that occurs only in certain parts of the body, such as the skin of the hands and face. CREST refers to the five main features of the syndrome: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Currently, there is no standard treatment for CREST syndrome, and there have been no studies of the use of traditional Korean medicine (TKM) for this disease. This study describes the effects of *Keumsuyukun-jeon* on CREST syndrome. The patient in this case had typical clinical symptoms of CREST syndrome. These symptoms improved within a relatively short period of receiving the TKM treatment. The results of Anti-centromere antibody (AI) and high sensitivity C-reactive protein (mg/L) also improved.

Key words: CREST syndrome, traditional Korean medicine, case report

Ⅰ. Introduction

Systemic sclerosis, often referred to as scleroderma, is a multi-organ disease characterized by structural abnormalities of blood vessels and fibrosis of organs such as skin, lung, heart, kidney, and digestive system caused by autoimmunity. This disease is classified as either diffuse cutaneous scleroderma or limited cutaneous scleroderma and are mainly seen in middle-aged women with a genetic background. The exact cause of the disease is not known, but it is understood that endothelial cell damage and fibroblast activity due to autoimmunity cause fibrosis of the tissue[1].

CREST syndrome is a form of limited cutaneous scleroderma that occurs only in certain parts of the body, such as the skin of the hands and face. CREST stands for the five main features of the syndrome, which are calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia[2].

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CREST syndrome is known to account for 22-25% of all scleroderma[3], and is a rare disease that occurs in approximately 2.7-19.3 per 1 million adults in the United States[4]. There have been few domestic and overseas studies, and none have been reported which traditional Korean medicine (TKM) treatments were applied. We report a case of typical CREST syndrome with improved clinical symptoms and blood test results after being treated with TKM treatment.

Ⅱ. Case

1. Patient symptoms and diagnosis

In January, 2017, a 49 year old female named Lee, ○○ visited the Korean internal medicine department of Daejeon University Korean Medicine Hospital for severe coughing with dyspnea, postprandial dyspepsia and received inpatient treatment for 22 days. The patient had been receiving treatment since being diagnosed with CREST syndrome at a tertiary General Hospital in 2012. Since a month before her first visit, her symptoms worsened to such an extent that she was unable to carry out everyday life after being overstressed at work. She had no history of trauma, surgery, alcohol, or smoking, and was taking vascular strengtheners, circulation improvers and ulcer remedies after the diagnosis in 2012.

She was 166 cm tall and weighed 57.7 kg at the time of admission, and her blood pressure was 150/90 mmHg, pulse 78 times/min, respiratory rate 20 times/min, and body temperature 37.0 ℃. In the physical examination, both hands showed scleroderma with skin thickened by progressed fibrosis, and calcification symptoms such as keratinization of the periphery of the lips were observed (Fig. 1, 2). Raynoud's phenomenon was observed at the extremities of the limbs as the environment changed. Esophageal dysmotility caused digestive symptoms such as postprandial discomfort and hunger sore and violent spasmodic coughing, and reddened vascular enlargement of the face and limbs was observed. Among her symptoms, the patient complained most about the coughing and digestive symptoms.

At the time of admission, the blood test results were mostly normal, but there were abnormality in the indexes related to autoimmune inflammation (Table 1). Urine analysis, chest X-ray and electrocardiography were also normal.

Table 1. Indexes Related to Autoimmune Inflammation

Indexes related to autoimmnity	Normal range	Level
Anti-nuclear antibody (Qualitative examination)	-	Positive
Anti-centromere antibody (AI)	0-1	1670
Erythrocyte sedimentation rate (ESR) (mm/hr)	0-20	16
High sensitivity C-reactive protein (hs-CRP) (mg/L)	0-1	1.69
Rheumatoid factor (RF) (IU/mL)	0-14	11.3

The patient had five typical clinical manifestations of the CREST syndrome: Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Her blood test revealed specific findings such as positive ANA and ACA, elevated CRP, and therefore, she was diagnosed with typical CREST syndrome.

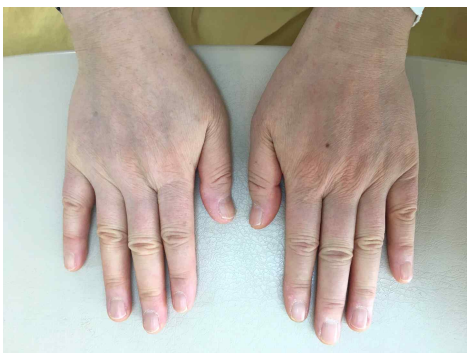

Fig. 1. Patient's hands.

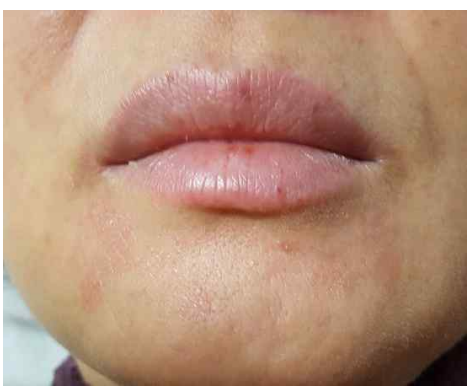

Fig. 2. Patient's mouth periphery.

2. Treatment and progress

From the first day of admission to the 22nd day of hospitalization, acupuncture treatment was performed twice a day, based on the oriental medicine theory. We used stainless steel needles having a thickness of 0.20 mm and a length of 15mm. The acupoints used were: L-9 (太淵), LI-7 (溫溜), PC-4 (郄門), GB-40 (坵墟), PC-8 (勞宮), GB-34 (陽陵泉), KI-10 (陰谷), SP-8 (地機), LU-5 (尺澤). 80 cc of *Keumsuyukun-jeon* (Table 2) was given to drink three times a day after meals. Moxa and hot packs were applied. Her usual treatment of Nicergoline 10 mg qd, Vitis vinifera ext. 150 mg and Rebamipide 100 mg bid were continually given to her.

The treatment was assessed by comparing the degree of spasmodic coughing and digestive symptoms, which were the most severe symptoms, during hospitalization. Visual analogue scale (VAS) was used as a method to objectify and quantify subjective symptom severity[5]. Cough symptoms gradually improved from VAS 9.2 at admission to VAS 5.0 on day 21. Digestive symptoms also improved from VAS 9.3 at admission to VAS 5.5 on day 21 (Fig. 3). Biochemical tests showed hs-CRP of 1.69 mg/L on the second day of hospitalization and 0.79 mg/L on day 20. The ACA was 1670AI on the second day of admission and decreased to 1360AI on day 20 of admission (Table 3).

The patient's subjective discomfort due to Raynaud's phenomenon was reduced to about 60% on the 22nd day of admission, and the overall condition felt by the patient also improved. However, there was no significant change in the appearance of scleroderma on both hands and the periphery of the lips between the time of admission and the 22nd day. The red dots on parts of the face and limbs remained. The patient was discharged on the 22nd day of hospitalization and is currently undergoing outpatient treatment and showing improved condition.

Table 2. Prescription of *Keumsuyukun-jeon*

Herbal name	Amount per day (g)
Rehmanniae Radix Preparata (熟地黃)	20
Angelicae gigantis Radix. (當歸)	8
Dinelliae Tuber. (半夏)	8
Poria cocas Wolf. (白茯苓)	8
Aurantii nobilis Pericarpium (陳皮)	12
Glycyrrhizae Radix. (甘草)	8
Brassicae Semen (白芥子)	6
Total	70

Table 3. Changes in Blood Test Results Associated with CREST Syndrome

	Normal range	Day 2	Day 20
Anti-nuclear antibody (Qualitative examination)	-	Positive	Positive
Anti-centromere antibody (AI)	0-1	1670	1360
High sensitivity C-reactive protein (mg/L)	0-1	1.69	0.79

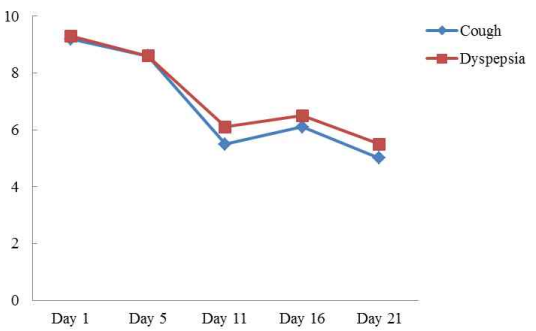

Fig. 3. VAS change of cough and dyspepsia.

Ⅲ. Discussion

Scleroderma is a systemic autoimmune disease that causes fibrosis of the skin, lungs, heart, kidneys, digestive system, skeletal muscle, and causes structural abnormalities of blood vessels. CREST syndrome, which is a type of limited cutaneous scleroderma, has five typical symptoms: Calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. To date, there is no cure for CREST syndrome, but immunosuppressants, antiplatelet agents, anti-fibrosis agents, and steroids are being used to relieve symptoms[6].

Although the cause is unknown, the disease seems tobe associated with anti-nuclear antibodies (ANA) and anti-centromere antibodies (ACA), with ANA being positive in 85% of patients with systemic sclerosis[7], and ACA, which is a more specific marker, seen in 82-96% of the patients with CREST syndrome[8]. Nonspecific indicators of inflammation, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are also relatively rare, but may increase in CREST syndrome[9]. Serial testing of autoantibodies to identify disease progression is generally not recommended, but there is clinical evidence that the titer of ACA is related to severity of vascular disease and Raynaud's phenomenon[10].

There has been little study done on CREST syndrome, which accounts of only 22 to 25% of systemic scleroderma, already a rare disease. Although there currently is no standard treatment for CREST syndrome, there is no study done on the use of TKM in this disease. Jang has reported using an electrogastrogram device for the improvement of digestive disorders[11] and Kim reported that the patient's skin and musculoskeletal symptoms improved with the pain assessment tool table in cases of systemic sclerosis[12], which is a larger category than CREST syndrome.

In this case, the patient was diagnosed with CREST syndrome at a tertiary General Hospital in 2012 and received continuous treatment. However, a month before admission, symptoms of cough and dyspepsia worsened to a point where every day life was impossible, and he visited our hospital seeking TKM treatment. At the time of admission, the patient showed subcutaneous calcification symptoms such as percutaneous skin changes and keratinization of the peripheries of the lips. When exposed to the cold or when under stress, numbness and itchiness of the extremity of the limbs, known as Raynoud's phenomenon appeared. Additionally, esophageal dysmotility caused nausea, digestive

symptoms such as dyspepsia, and severe spasmodic cough. Telangiectasia with redness was observed on areas of the face. Immunohistochemistry showed that ANA and ACA were positive and elevated hs-CRP was also observed, diagnosing the patient with typical CREST syndrome.

To restore esophageal function, acupuncture was performed twice a day according to TKM theory. *Keumsuyukun-jeon* is administered to weak patients who are breathless after coughing and suffer from nausea, and has been reported in animal studies to restore respiratory mucosal abnormalities and to inhibit allergic reactions and infiltration of inflammatory cells[13-15]. In Korean traditional medicine, the crest syndrome patient was diagnosed to have insufficient moisture in the body. So we selected the acupuncture points that add moisture to the skin and muscles. *Keumsuyukun-jeon* was also used for adding moisture to the body.

This patient had progressive improvement of spasmodic cough symptoms and indigestion symptoms during admission. Each VAS also gradually improved, but when the patient was exposed to stress due to personal problems on the 15th day after admission, all the symptoms became worse and the VAS score increased. Scleroderma, like other autoimmune diseases, is known to develop or worsen under stress or environmental changes[16], and the patient also experienced disease aggravation after severe stress in the workplace a month before admission.

Blood tests showed that the activity of ACA, the most specific marker of CREST, was also reduced by about 20%, and the elevated hs-CRP decreased to normal range on the 20th day after admission. A clinical observation by Buchanan RR et al reported that ACA activity is correlated with Raynaud's syndrome and vascular disease[10], and suggests that the ACA titer reduction in this patient is meaningful for the patient's prognosis improvement. CRP, which is also a nonspecific indicator of inflammation, is a marker for the progression of various autoimmune diseases , and reductions in CRP indicate reduced autoimmune activity[17].

In relation to the safety of this treatment, no adverse effects such as skin damage or inflammation were observed during acupuncture treatment, and no side effects due to herbal medicine were observed. Blood tests performed on the 20th day of admission showed no significant change in liver function tests, renal function tests, and urinalysis compared to those done on admission.

The limitation of this study is that it is difficult to identify the effect of TKM alone on CREST syndrome as the patient received both TKM and western medicine treatment simultaneously. However, the patient's western medication was taken continuously for 5 years ever since the diagnosis was first made in 2012, and the effect is thought to be weak considering the fact that the symptoms have worsened through out the treatment. TKM treatment with acupuncture and herbal medicines improved both the subjective symptoms of the patient and related indicators on the blood test within a relatively short period of 3 weeks and was safe without side effects. The authors wish to expand the baseline of TKM for rare diseases through this case and report that oriental treatment for CREST syndrome was effective.

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