Scleroderma and Repeated Spontaneous Abortions Treated with Vitamin E — A Case Report —

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Summary: A 33-year-old woman was referred to our hospital due to repeated spontaneous abortions and positive autoantibodies. She had noticed Raynaud's phenomenon 13 years earlier. We diagnosed scleroderma based on the presence of Raynaud's phenomenon, proximal scleroderma, presence of anti-centromere antibodies, and histological findings on skin biopsy. Neither lupus anticoagulant nor anti-cardiolipin- β 2-glycoprotein 1 antibody was detected. We administered tocopherol nicotinate. Five months after the initiation of the treatment, she became pregnant and later delivered a healthy baby.

Key words pregnancy, scleroderma, spontaneous abortion, tocopherol, vitamin E

INTRODUCTION

Scleroderma, also known as systemic sclerosis, is an autoimmune disorder characterized by connective tissue fibrosis and diffuse vasculopathy. The pathogenesis of scleroderma, a complex life-threatening systemic disease that targets the skin, lungs, heart, gastrointestinal tract, peripheral circulation, and musculoskeletal system, is incompletely understood [1]. The incidence of scleroderma is higher among women than among men. This female predominance raises the issue of the outcome of pregnancy in the affected women. Scleroderma ordinarily affects women in the late reproductive and post-reproductive age. Therefore, pregnancy in patients with scleroderma is relatively rare. However, the incidence of pregnancy in affected patients is increasing, because recently many women are delaying childbearing [2-5]. Therefore, obstetricians and physicians need more information about pregnancy in women with scleroderma.

Many drugs have been used for the treatment of scleroderma [1]. Although scleroderma cannot be completely cured, treatment of the involved organs can improve their functions and relieve symptoms.

We describe a woman with scleroderma, who had experienced spontaneous abortion twice, but successfully delivered a healthy baby after treatment with vitamin E.

CASE REPORT

A 33-year-old Japanese female was referred to our hospital in February 2003 because of repeated spontaneous abortions. She had married at the age of 29 years and had experienced spontaneous abortions at the age of 30 and 32 years. On examination by a local obstetrician, there was no abnormality in the uterus or ovaries. The doctor referred her to our rheumatology unit because of positive anti-nuclear and anti-centromere antibodies. She had noticed Raynaud's phenomenon in 1990. However, she did not have any other symptoms. Physical examinations demonstrated a temperature of 36.4 °C, heart rate of 72 beats/min, respiration rate of 16/min and blood pressure of 120/80 mmHg. Pulmonary auscultation did not detect any abnormality. The abdomen was soft, not tender, and without organomegaly. No lymphadenopathy was noted. The skin on her fingers, hands and forearms appeared slightly shiny and taut.

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TABLE 1.
Laboratory data on admission

Hematology	BUN	9.2 mg/dL
WBC 3900/mm ³	Creatinine	0.59 mg/dL
neutrophils 42%	Immunological examination	
lymphocytes 50%	IgG	2290 mg/dL
monocytes 7%	C3 (72-144)	95 mg/dL
eosinocytes 1%	C4 (10-40)	13 mg/dL
RBC 534×10 ⁴ /mm ³	RF	(+)
Platelet 21.5×10 ⁴ /mm ³	HBs-antigen	(-)
Urinalysis	anti-HBc antibody	(-)
nothing particular	anti-HCV antibody	(-)
ESR 29 mm/hr	anti-HTLV1 antibody	(-)
Biochemical examination	anti-nuclear antibody	(+)
AST 15 U/L	anti-DNA antibody	
ALT 12 U/L	ds	(-)
LDH 159 U/L	ss	(-)
ALP 175 U/L	anti-U1 RNP antibody	(-)
γ-GTP 24 U/L	anti-SSA antibody	(+)
Total protein 8.92 g/dL	anti-centromere antibody	(+)
Albumin 4.94 g/dL	lupus anticoagulant	(-)
CRP 0.08 mg/dL	anti-cardiolipin-β2GP1 antibody	(-)
CK 53 mg/dL		

WBC : white blood cell; RBC: red blood cell; ESR: erythrocyte sedimentation rate

AST : aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase

ALP : alkaline phosphatase; γ-GTP: gamma-glutamyl transpeptidase; CRP: C-reactive protein

CK : creatine phosphokinase; BUN: blood urea nitrogen; IgG: immunoglobulin G; C: complement

RF : rheumatoid factor; GP: glycoprotein

Chest radiography did not show any abnormality. Laboratory findings are shown in Table 1. She was positive for rheumatoid factor, anti-nuclear antibody, anti-centromere antibody and anti-Ro/SSA antibody, but negative for anti-U1-RNP antibody or anti-Scl70 antibody. Activated partial thromboplastin time was normal. Neither lupus anticoagulant nor anti-cardiolipin-β2-glycoprotein1 antibody was detected. Therefore, it was unlikely that spontaneous abortion was due to antiphospholipid syndrome. Skin biopsy was performed from the forearm and the specimen demonstrated a thin epidermis and an increase in collagen fibers. We diagnosed her as having an especially limited cutaneous scleroderma based on the presence of Raynaud's phenomenon, proximal scleroderma, serological abnormality and histological findings [6]. No visceral involvement was recognized. Because she desired a child, we administered 300 mg/day of tocopherol nicotinate from June 2003. She became pregnant in November 2003. Her prenatal course was uneventful, and she remained in a

stable condition during the pregnancy. A baby was delivered in August 2004 after 41 weeks of pregnancy. The baby weighed 3,284 kg and erythema was recognized on his back. No cardiac abnormality was recognized. Thereafter, the patient has been followed at our outpatient department and remains in a stable condition.

DISCUSSION

We report a female patient with scleroderma who experienced spontaneous abortions twice. Reports of the outcomes of pregnancies in women with scleroderma have been quite variable. Some literature reported that mothers and infants both had poor outcomes [2,3], while others reported optimistic outcomes [4,5,7].

The antiphospholipid syndrome is associated with recurrent miscarriage in patients with autoimmune diseases. The pathogenesis of pregnancy loss in antiphospholipid syndrome is thought to be linked

to placental thrombosis [8]. However, the present patient was negative for lupus anticoagulant and anti-cardiolipin- β 2 glycoprotein1 antibody, and activated partial thromboplastin time was normal. Therefore, the association of antiphospholipid syndrome was unlikely in the present patient.

The anti-Ro/SSA antibody is strongly associated with neonatal lupus including congenital heart block [9]. Furthermore, this antibody may affect the pregnancy of the mother with this antibody. The pregnancy rate, ongoing pregnancy and live birth rate did not seem to be influenced by the presence of the anti-Ro/SSA antibody in patients with systemic lupus erythematosus (SLE). However, the antibody is associated with recurrent pregnancy loss in non-SLE patients including those with scleroderma, Sjögren syndrome and rheumatoid arthritis [10]. The present patient was positive for anti-Ro/SSA antibody. Therefore, this antibody might be associated with spontaneous abortion. However, the detailed mechanism of this phenomenon in patients with scleroderma has not yet been clarified.

The cause of spontaneous abortion in patients with scleroderma is not fully understood. The pathogenesis of scleroderma is thought to involve autoimmunity, abnormal fibroblastic collagen production and endothelial abnormalities. This disease involves various internal organs [1]. The placenta, which embodies the maternal-fetal interface, may be affected in patients with scleroderma. Decidual vasculopathy in the placentas has sometimes been observed in maternity patients with scleroderma [11,12]. Therefore, these vascular abnormalities may induce ischemia of the placenta and may be associated with a poor pregnancy outcome in some patients with scleroderma.

Many drugs have been used to treat scleroderma. To improve the vasculopathy, antiplatelet agents, calcium channel blockers, serotonin antagonists and prostaglandin analogues are used. However, some of these are not suitable for pregnant women. Vitamin E, a major lipid-soluble antioxidant, has been shown to have significant benefits in preventing a variety of diseases. Vitamin E is known to occur in nature in eight different forms including tocopherols and tocotrienols [13]. Tocopherols and tocotrienols have properties of antioxidants and anti-platelet aggregation agents [14], and are protective against ischemic tissue damage [15]. Therefore, vitamin E may have a protective effect on the ischemic placenta induced by decidual vasculopathy, although further detailed

studies with a large number of patients are needed before drawing conclusions on this hypothesis.

In conclusion, we report a woman with scleroderma, who experienced spontaneous abortion twice, then successfully delivered a healthy baby after the administration of vitamin E. Vitamin E might be a useful agent for women with scleroderma who experience spontaneous abortion.

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