Improvement of Progressive Systemic Sclerosis (PSS) with Estriol Treatment

HIROSHI KATAYAMA, KIYOSHI OHSAWA and HIDEO YAOITA

Department of Dermatology, Jichi Medical College, Tochigi, Japan

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Two female patients suffering from progressive systemic sclerosis (PSS) of generalized type were treated with estriol for 10 months. Although complete cure was not achieved, considerable beneficial effects were observed in these patients, but no serious side effects. Thus, skin softening was observed on all involved parts of these patients, which was accompanied by increased mobility of large or medium-sized joints and improved pigmentation and cyanotic redness on fingers and extremities. However, no apparent improvement of internal organ involvement could be detected. Histopathologically, a drastic reduction of homogenization of collagen bundles in the dermis of affected forearms was seen in these patients following estriol treatment. To our knowledge this is the first report of estriol therapy for PSS. *Key words: Homogenization of collagen bundles.* (Received June 30, 1983.)

H. Katayama, Department of Dermatology, Jichi Medical College, Tochigi, Japan.

Progressive systemic sclerosis (PSS) is thought to be a disorder of connective tissue which affects not only the skin but also a variety of internal organs. Its pathogenesis is still unknown (1, 2). Although a few drugs are known to affect the course of this disease (1, 3), a complete cure is as a rule not expected (4). The following facts happened to make us consider estriol therapy for PSS. Firstly, PSS affects primarily women (4). Secondly, pregnancy sometimes shows a favorable effect on PSS (5, 6, 7). Thirdly, estriol comprises the greater part of urinary estrogen in late pregnancy (8). Fourthly, estriol has a softening effect on the cervix uteri during parturition. Lastly, estriol inhibits osteoporosis (9), which is not only an aging effect but also one of the clinical manifestations of PSS. To our knowledge, estriol therapy for PSS has not been reported before. We describe here the results of such treatment.

CASE REPORTS

Two patients with PSS who gave prior informed consent were treated with estriol. Their diagnosis was confirmed by clinical and histopathological investigations. In these patients, cutaneous involvement was found on the trunk and extremities (generalized type). Examinations made included erythrocyte sedimentation rate (ESR), urinalysis, blood count, blood chemistry, serological tests, X-ray examination of chest, gastrointestinal tract and hands, pulmonary function tests, electrocardiogram, sialography and so on.

According to the American Rheumatism Association's proposal of "proximal scleroderma" as the sole major criterion of systemic sclerosis, whose sclerodermatous cutaneous changes were defined as tightness, thickening and non-pitting induration (10), we made much of inspection and palpation when assessing cutaneous involvement, e.g. on pigmentation, wrinkle formation, the degree of skin being lifted by fingers and so on. As PSS usually begins with edema or swelling of fingers and progresses to hidebound changes (1, 11), we classified cutaneous involvement into five stages as follows: stage 0 =

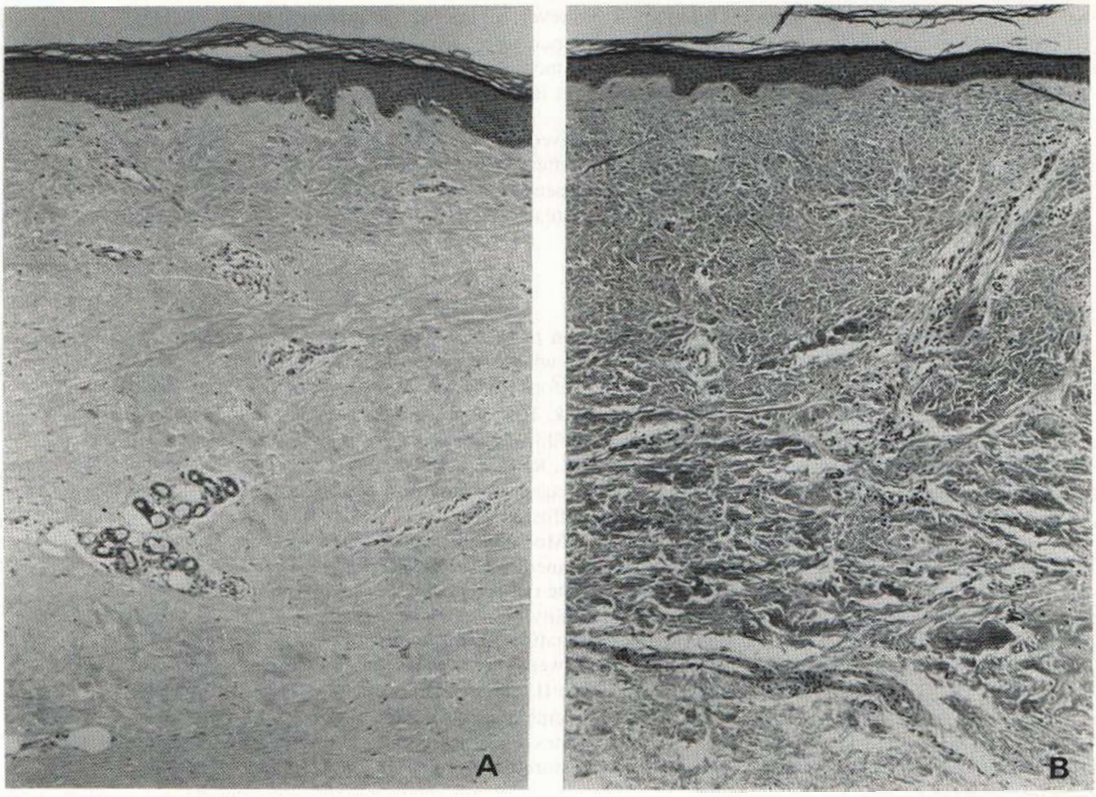

Fig. 1 A. The specimen obtained from extensor aspect of right forearm in case 1 before estriol treatment. Dermal thickening and homogenization of collagen bundles are remarkable (HE, ×40).

Fig. 1 B. The specimen obtained from the area closely adjacent but peripherally situated (in the direction of more severe involvement) to specimen (A) after 10 months of estriol treatment. Homogenization of collagen bundles in the dermis has almost disapppeared, leaving slight interstitial edema and only partial swelling of collagen bundles in deep dermis (HE, ×40).

normal skin, stage I = barely traceable involvement, stage II = edema or swelling, stage III = scleroedematous change (intermediate between stage II and stage IV), and stage IV = sclerosis (tightness, thickening and non-pitting induration).

Case 1

A 48-year-old woman developed swelling and stiffness of her fingers in December 1978, which spread gradually to involve face, forearms and lower legs, associated with occasional episodes of arthralgia of wrists and knees. After a diagnosis of PSS was made, several drugs such as vasodilators, proteinases, penicillamine and glucocorticoid were administered, but almost without effect. In June 1982, just before estriol therapy was tried, sclerosis or scleroedematous change was present on face, midchest, fingers, hands, arms, legs and feet. She could neither stretch her fingers nor flex her knees fully. Laboratory study disclosed the following abnormalities: increased ESR, IgG, LDH and ZTT, positive RA and occasionally positive CRP. There was acro-osteolysis of fingers and bibasilar pulmonary fibrosis, together with decreased gas diffusion. Sialography suggested a combination of Sjögren's syndrome.

Subcutaneous injection of estriol (Estriel Depot®, Mochida Pharmaceutical Co., Tokyo, Japan), 10 mg/week, caused significant improvement of the cutaneous involvement, namely, slight softening of the extensor aspect of the left forearm, beginning as early as 1 week after the first estriol injection. After 10 months of treatment, involvement of stage IV or stage III seen on the face, extremities and trunk improved to stage I or stage II, except for the dorsum of the right hand and fingers, which had

been most severely involved. Even on these areas, however, an improvement from stage IV to stage III indicated apparent improvement, which was accompanied by a reduction in pernio-like redness, pigmentation and depigmentation. There was increased mobility of the knee joints, but the finger joint contractures were only slightly improved. No apparent improvement in internal organ involvement was yet detected.

Fig. 1 (A and B) shows the histopathology of the involved skin obtained from the extensor aspect of right forearm before and after 10 months of treatment. After treatment, remarkable homogenization of collagen bundles—which had been present before treatment—almost disappeared, leaving only partial swelling of collagen bundles in the deep dermis and instead, slight interstitial edema was seen in the entire dermis.

Case 2

A 59-year-old woman developed Raynaud phenomenon in fingers in February 1980. Within a few months, she noted edema and stiffness of the fingers, which spread subsequently. No drugs could prevent the disease from progressing and just before estriol administration in June 1982, hidebound change was seen on the extremities and trunk. Her weight had decreased by 6 kg since the onset of the disease. Laboratory study disclosed the following abnormalities: increased ESR, LDH, IgG, CPK, and serum creatine, slightly depressed WBC, RBC and Hb counts, positive RA, as well as occasionally positive ANF and CRP. There was esophageal hypomotility, acro-osteolysis in fingers and bibasilar pulmonary fibrosis with decreased gas diffusion.

Treatment was started with peroral estriol (Estriel®, Mochida Pharmaceutical Co., Tokyo, Japan), 2 mg/day, for a month and then changed to subcutaneous estriol injection (Estriel Depot®), 10 mg/week, for 3 months and 20 mg/week thereafter, as she refused further estriol ingestions because of the occurrence of urticaria. She noticed increased mobility of neck and extremities as early as 4 days after commencing the treatment, and slight wrinkle formation on the dorsum of right hand joint after 1 month. After 10 months of treatment, improvements were observed as follows: dorsum of fingers (from stage IV to partly stage III combined with stage II and stage I), dorsum of hands, forearms, midchest and face (from stage III to partly stage I combined with stage II), back, hip and lower extremities (from stage IV to stage III). Cyanotic redness on fingers and extremities was reduced. However, finger joints contractures were scarcely restored and apparent improvement of internal organ involvement could not be detected.

Histopathological examinations showed a similar change as in case 1. That is, the specimen taken from the extensor aspect of the left forearm after 10 months of treatment revealed remarkable improvement of the homogenization of collagen bundles that had existed before treatment.

DISCUSSION

Single administration of estriol caused apparent skin softening within 10 months in the patients studied. Amazingly, the patient in case 2, who was most severely involved, noted increased mobility of extremities as early as 4 days after estriol ingestion and the patient in case 1 noted incipient skin softening one week after the first estriol injection. Improvement occurred initially in the area of slight involvement and then in the more severely involved areas. Although complete cure was not obtained, skin softening was observed in all involved areas of these patients within 10 months of treatment, which was accompanied by increased mobility of large or medium-sized joints and improvements in pigmentation and cyanotic redness on fingers and extremities. However, flexion contractures of fingers were rather recalcitrant. This is probably because the fibrotic dermis had fused firmly with tendons, joint capsules and periosteum, as Asboe-Hansen indicated (12).

The most remarkable histopathological changes after estriol therapy was the reduced homogenization of collagen bundles (11).

Definite improvement in internal organ involvement and laboratory data was not detected within 10 months of commencing our study. Side effects were observed only in patient no 2, who had urticaria for a month and menses-like bleeding for a week, which she had never experienced since she was 38 years old. Gynecological examinations revealed no particular abnormalities.

The mechanism of estriol action as well as estradiol and estron on connective tissue in systemic scleroderma is still obscure because of the scarcity of basic biological data in this field (13, 14). We must wait for further investigation.

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