□ CASE REPORT □

Ehlers-Danlos Syndrome Combined with von Recklinghausen Neurofibromatosis

Teruto HASHIGUCHI, Ikuro MARUYAMA*, Ken SONODA, Hiroaki NAKASHIMA, Naoto NAKAMURA**, Yoshito SONODA and Mitsuhiro OSAME*

We recently had the opportunity to study a 25-year-old male with both Ehlers-Danlos syndrome (EDS) and von Recklinghausen neurofibromatosis (VRNF). We describe the clinical manifestations of the case and discuss the probable pathomechanism of the combination of the two syndromes, with a review of the literature. As recent literature suggests that both syndromes are linked to chromosome 17, we conclude that their combination is not coincidental, but genetically linked.
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Key words: chromosome 17

Introduction

Ehlers-Danlos syndrome (EDS) is a heritable disorder of the connective tissue characterized by hyperextensible skin, hypermobile joints, fragility and bruisability of the skin, with "cigarette paper" scarring and generalized tissue fragility. von Recklinghausen neurofibromatosis (VRNF) is a heredofamilial disease characterized by cutaneous pigmentation and multiple tumors arising from elements of the peripheral and central nervous system, as a result of dysgenesis of the primitive ectoderm (1). Recently we had a case with features of the two syndromes. Here, we describe the clinical and laboratory findings of this case and discuss the pathomechanism of the combination of these two heritable disorders.

Case Report

A 25-year-old male was admitted to our hospital on January 16, 1989, with the complaint of swelling of his right leg. After emergency admission, the right leg swelling gradually increased and he became semiconscious, suffering preshock and anemia. The past history was significant in that his mother had noted at birth the presence of brown pigmented areas (café-au-lait spot) over his body. The mother also stated that the patient did not walk until the age of two years, and had a bleeding tendency since childhood, which was characterized by easy bruising with hematoma formation following minor trauma. The patient had no children; examination of his mother and five siblings revealed no clinical signs or symptoms associated with EDS or VRNF. His father was alive and well but could not be examined. Consanguinity and illegitimacy were denied. The patient was 141.0 cm tall, arm span 150.0 cm, and weight 32.4 kg. His blood pressure was 100/40 mmHg on emergency admission; after an hour it had dropped to 80/40 mmHg. Pulse rate was 90 beats/min and regular, respiration 25/min and temperature normal. Multiple café-au-lait spots were present all over the body, associated with a few nodules on the forehead and anterior region of the chest. Examination of the extremities revealed hyperextensibility of finger, shoulder, ankle and joints. The skin was unusually soft and silky, and could be stretched for several centimeters and on release would immediately spring back into its former position. In the mouth, there was gingival hyperplasia, the typical high-arched palate. The subcutaneous fat was sparse, and the muscles were poorly developed and hypotonic. He had a pronounced pectus carnatum. The other physical examinations were normal. Radiography demonstrated mild scoliosis of the lumber spine, and severe generalized osteoporosis.

Biopsy of a nodule on the anterior region of the chest showed the typical findings of a neurofibroma (Fig. 1). It was composed of thin, wavy fibrils, lying loosely together and tending to form whirls. Between these fibrils were a

From the Department of Internal Medicine, Kagoshima Medical Association Hospital, Kagoshima, *the Third Department of Internal Medicine, Kagoshima University, School of Medicine, Kagoshima and **Iwao Hospital, Kagoshima
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Reprint requests should be addressed to Dr. Teruto Hashiguchi, the Department of Internal Medicine, Kagoshima Medical Association Hospital, 7–1, Kamoikeshinmachi, Kagoshima 890, Japan

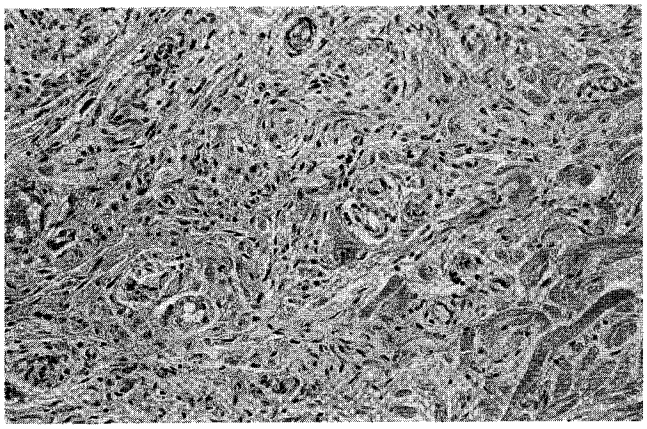

Fig. 1. Biopsy specimen of a nodule showing the typical findings of a neurofibroma (×400; hematoxylin and eosin stain).

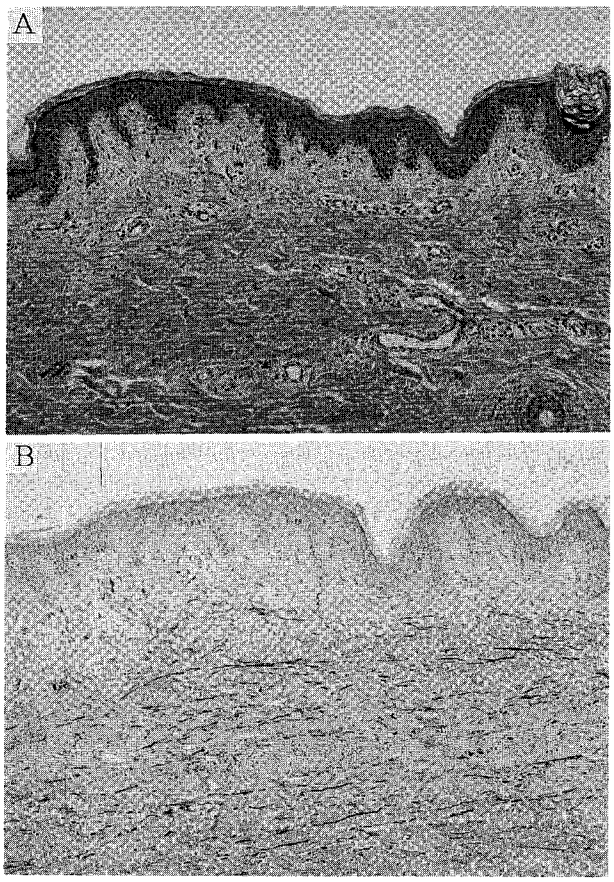

Fig. 2. A skin biopsy from the left thigh showing no abnormal findings in the histologic composition of the collagen (A: ×200; hematoxyline and eosine stain) and elastic fibers (B: ×200; Weigert stain).

fairly large number of nuclei which were small, uniform in size, oval to spindle-shaped and rather palely stained. A skin biopsy from the left thigh stained with hematoxylin and eosin (Fig. 2-A) or Weigert stain (Fig. 2-B) showed the dermis to be composed of relatively dense collagen-tissue; elastic fibers were numerous among the collagen fibers and did not appear to be degenerated. There seemed to be no abnormality in the histologic composition of the elastic or collagen fibers. The results of routine laboratory tests on admission, shown in Table 1, reveled the presence of slight hypochromic anemia. Liver function test results were as follows: serum glutamate oxaloacetate transaminase, 28.5 K-U(10.0−33.0); serum glutamate pyruvate transaminase, 10.1 K-U(5.0−27.0); serum alkaline phosphatase, 10.3 K-A-U(4.0−11.0); serum choline esterase, 0.7 Δ PH(0.6−1.2) and serum total bilirubin 0.9 mg/dl(0.2−1.0). The level of serum urea nitrogen and serum creatinine were normal; urinalysis showed a trace of protein, no blood cells and abnormal sediment.

Table 1. Hematological Data on Admission

White blood cells	145×10^2 (/mm^3)
Red blood cells	397×10^4 (mm^3)
Hemoglobin	11.1 (g/dl)
Hematocrit	33.7 (%)
Platelets	26.1×10^4 (/mm^3)
Serum total protein	6.9 (g/dl)
creatinine	1.2 (mg/dl)
urea nitrogen	19.6 (mg/dl)
sodium	137 (mEq/l)
chloride	98 (mEq/l)
potassium	4.8 (mEq/l)
amylase	154 (s−u)
blood sugar	148 (mg/dl)
C-reactive protein	negative

Hemostatic parameters of the patient on emergency admission were abnormal; many coagulation factors, including fibrinogen, were decreased (data not shown). This abnormality was thought to be due to massive hemorrhage and preshock state, since the profile of the coagulation fibrinolytic examination after recovery from the emergency was almost normal (data not shown), including the plasma fibronectin level. Cytogenetic analysis of white blood cells by the G-banding technique revealed no abnormalities.

Discussion

EDS and VRNF are both well characterized diseases. The incidence of VRNF is 1 in 3000, with autosomal dominant inheritance (2). The incidence of EDS is much less than that of VRNF; however, at least 10 types of EDS have been defined, and about half of the patients with signs of this syndrome do not meet the criteria for any of the 10 types (3). VRNF has many associated disorders, such as malignant shwannoma and pheochromocytoma (4). The present case is a combination of EDS, type unspecified, and VRNF. At present in the literature, there are 4 cases (5−8) with these two syndromes combined but the pathomechanism or genetic background is not described. The question of whether these two syndromes are a coincidental occurrence, or

are parallel results of a single primary disturbance in embryonic development, remains to be elucidated. Recently it was demonstrated that the VRNF gene is genetically linked to the locus encoding the nerve growth factor receptor located on the long arm chromosome 17 in the region 17q12→17q22 (9). Another report describes the human pro-α1(I) collagen gene as also being located in chromosome 17 and localized in 17q21→17qter (10). These results suggest the probability that the combination of EDS and VRNF is not coincidental but is the result of a similar mechanism involving chromosome 17; however, the feasibility of this mechanism remains to be elucidated at the gene level.

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