Two Cases of Myocardial Infarction in Type 4 Ehlers-Danlos Syndrome

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Ehlers-Danlos syndrome is an inherited connective tissue disorder. Clinical manifestations of this syndrome are due to fragile connective tissue. Though many cardiovascular disorders in association with it have been reported, myocardial infarction is quite rare. In this report, two cases with type 4 Ehlers-Danlos syndrome and myocardial infarction are described. Patient 1 was a 30-year-old woman. She was diagnosed as having myocardial infarction on the basis of typical changes in electrocardiograms and serum enzymes (CPK, SGOT and LDH). The diagnosis of type 4 Ehlers-Danlos syndrome was made by the microscopic examination of her connective tissue. Patient 2 was a 32-year-old man. He was also diagnosed as having acute myocardial infarction. His fibroblasts were cultured and they could not synthesize type 3 collagen. Type 4 Ehlers-Danlos syndrome was diagnosed. It was likely that myocardial infarction might have resulted from the fragility of their coronary arteries in type 4 Ehlers-Danlos syndrome.

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Ehlers-Danlos syndrome is an inherited connective tissue disorder which is manifested by hypermobility of joints, hyperextensibility of the skin and other clinical manifestations due to fragile connective tissue.1,2 In contrast to other forms of this syndrome, patients with type 4 Ehlers-Danlos syndrome have fragile but inextensible connective tissue, and their major clinical manifestations are related to the cardiovascular system and gastrointestinal tract.3,4 Review of the literature indicates that myocardial infarction in type 4 Ehlers-Danlos syndrome is quite rare. In this report, two cases with type 4 Ehlers-Danlos syndrome and myocardial infarction are described. The pathogenesis remains uncertain, but fragility of coronary arteries in these patients was thought to be related to myocardial infarction.

CASE REPORTS

Case 1

A 30-year-old woman was admitted to our hospital to undergo cardiac catheterization. Until 22 years old, she had undergone operations for dislocation of bilateral hip joints six times. At the age of 17 years, spontaneous hematemesis occurred, but the source of bleeding was unknown. Her parents and brother did not show any abnormalities of connective tissue and did not suffer from myocardial infarction. In February 1982, chest pain suddenly occurred during sleep, and she became unconscious. She then was admitted to a local hospital. The electrocardiogram showed ST elevations in leads 2, 3, aVF, and V5 to V6. The creatine value was 719 U/L, SGOT was 320 U/L, and LDH was 1,067 U/L on admission, which showed serial changes. Acute myocardial infarction was diagnosed and intensive care begun. Her condition gradually improved and two months after the episode she could walk in the hospital. She was admitted to our hospital for cardiac catheterization in April 1982. Initial physical examination revealed a slightly plump woman with relatively slender extremities. On cardiac examination, her heart sounds were normal. An ejection systolic murmur was audible. There was no thrill, carotid bruit, jugular venous distension, hepatosplenomegaly, cyanosis, clubbing, or peripheral edema. The chest radiograph showed a normal cardiac silhouette with a cardiothoracic ratio of 47.8 percent. The electrocardiogram showed normal sinus rhythm, normal axis, poor R wave progression in the precordial leads, and coronary T wave inversions in leads 3, V5 to V6. The two-dimensional sector scan of ultrasound disclosed wall motion abnormality (hypokinesis) at the anteroseptal wall. Thallium myocardial perfusion imaging revealed an apical defect. The bleeding time, coagulation time, prothrombin time, and partial thromboplastin time were all normal, but a Rumpel-Leede test was moderately positive, which suggested fragility of vessels. Other laboratory studies showed a negative rheumatoid factor and lupus erythematosus preparations, normal serum protein electrophoresis, and immunoglobulin, C3, C4, and antinuclear antibody. On May 13, cardiac catheterization was tried through the femoral approach, but massive hemorrhage occurred at the puncture site and then it was stopped. On June 2, the second catheterization was tried with the Sones method. When the right brachial artery was exposed, the artery suddenly ruptured without any aggressive procedures. An attempt was made to suture the ruptured artery but it was so fragile that it could not be reconstructed. We had no other alternative but to occlude the artery. A few weeks later, we performed biopsy of the anterior branch of the left temporal artery. In light microscopy, all the dermis appeared looser than normal with the presence of thinner, more spaced apart and more irregularly oriented collagen fibers. Moreover, the elastic component was very developed, chiefly in the reticular dermis, where it consisted of long and thick fibers. Microscopic examination of the arteries from the patient revealed a characteristic thickening of the intima. The stromal space between the endothelial lining and the elastic lamina was characterized by...
the presence of a profuse amorphous material associated with multilaminated basal lamina beneath the endothelial cells.

Diagnosis of type 4 Ehlers-Danlos syndrome was made. Two months later she was discharged without necrosis of her right arm.

Case 2

A 32-year-old man was admitted to our hospital because of chest pain and dyspnea. From childhood he bruised easily, but his skin was not excessively fragile and formed normal scars. Spontaneous hemothorax occurred at the age of 16 years, and he received drainage and blood transfusion. His relatives did not suffer from any connective tissue disorders or myocardial infarction. In July 1985, he was struck on the chest with something in a crowd. Several hours later, mild dyspnea and chest pain developed, and he was admitted to a nearby hospital. The chest radiograph was normal. The electrocardiogram showed ST elevations in leads 1, aVL, and V1 to V4 (Fig 2A). On the following day, he was admitted to our hospital. Initial physical examination revealed blood pressure of 130/86 mm Hg without pulsus paradoxus, a regular pulse of 90 beats per minute and normal respirations. A round ecchymosis was noted on the chest wall but no tenderness. Superficial veins were easily visible. Normal first heart sound, normal second sound, and a soft ventricular gallop (S3) were audible. There was no murmur, thrill, carotid bruit, jugular venous distention, hepatomegaly, cyanosis, clubbing, or peripheral edema. The electrocardiogram showed normal sinus rhythm, normal axis, and ST elevations in leads 1, aVL, and V1 to V4 (Fig 2A). On the tenth hospital day the electrocardiogram showed pathologic Q waves in leads 1, aVL, and V1 to V4 and coronary T wave inversions in leads 1, 2, 3, aVF, and V1 to V4 (Fig 2B). The two-dimensional sector scan of ultrasound disclosed wall motion abnormality (hypokinesis or akinesis) at the anteroseptal wall. On the third hospital day 99m technetium pyrophosphate scintigraphy revealed abnormal uptake, and two weeks later thallium myocardial perfusion imaging revealed an anterolateral defect. The maximal creatine kinase value was 2,200 U/L and the MB fraction was 180 U/L, and they showed serial change. These findings were compatible with acute myocardial infarction. Other laboratory studies showed no anemia, normal bleeding time and coagulation time. The prothrombin time and the partial thromboplastin time were also normal. But a Rumpel-Leede test was moderately positive. It suggested fragility of the vessels. The chest radiographs showed a huge mass shadow at the left lung field. The CT scan disclosed that it was intramedialateral bleeding. Two months later the hematoma was completely absorbed. The digital subtraction angiography showed an aneurysm of the abdominal aorta. It was calcified in the CT scan, suggesting an old aneurysm.

We performed biopsy of a frontal branch of the superficial temporal artery. Microscopically, collagen fibers were very scanty and striation of the internal elastic membranes was noted (Fig 3). Electron microscopic examination showed rupture of the internal elastic membrane and invasion of myofibroblasts into the intima. These findings were compatible with type 4 Ehlers-Danlos syndrome. His fibroblasts were cultured. They could not synthesize type 3 collagen (Fig 4A).**

The patient's subsequent recovery was uneventful without any
resulting in intramyocardial hemorrhage. Clinical and laboratory findings between cardiac contusion and myocardial infarction are similar. Serum cardiac enzyme levels may be elevated, radionuclide imaging may be abnormal, and there may be abnormal wall motion in both conditions. Thus, it is difficult to differentiate them. However, electrocardiograms might be helpful to differentiate them. Potkin et al. examined 100 patients with blunt chest trauma. Seventy-two patients had apparent cardiac contusion. However, no patient had a Q wave in the electrocardiogram. Thus, we think that he had myocardial infarction rather than cardiac contusion, although we cannot deny the possibility of contusion.

Either case had no episode of angina pectoris. They were young to experience myocardial infarction due to coronary atherosclerosis, at least in Japan. Of course, they had none of the so-called coronary risk factors—hypertension, diabetes mellitus, hyperlipidemia, etc. Thus, the pathogenesis of myocardial infarction became the subject of discussion. Both cases showed normal bleeding time and coagulation time. There were no other abnormal laboratory studies but the positive Rumpel-Leede test. They had neither hyperextensibility of the skin nor hypermobility of joints. Case 1 had a history of dislocation of bilateral hip joints and spontaneous hematemeses, and on cardiac catheterization her arteries were so fragile that they spontaneously ruptured. Case 2 also had a history of spontaneous hemothorax, and supervisible veins were noted. Those findings suggested some connective tissue disorder.

We performed biopsy of the anterior branch of the left temporal artery. Microscopically collagen fibers of the dermis of case 1 were thinner, more spaced apart and more irregularly oriented than normal. The intima of her arteries was thickened and the characteristic material was observed beneath the intima (Fig 1). Although we could not perform biochemical studies, she was obviously diagnosed as having type 4 Ehlers-Danlos syndrome according to the microscopic findings and clinical manifestations. The diagnosis of type 4 Ehlers-Danlos syndrome was biochemically obvious in case 2 because his fibroblasts could not synthesize type 3 collagen.

We could not perform cardiac catheterization, so the pathogenesis of myocardial infarction was unclear. But the fragility of coronary arteries, in association with type 4 Ehlers-Danlos syndrome, may have been related to myocardial infarction.

Ehlers-Danlos syndrome is an inherited connective tissue disorder. This syndrome now is subdivided into at least ten types on clinical and biochemical grounds. The type 4 syndrome is characterized by a specific deficiency of type 3 collagen in tissues and cultured fibroblasts of patients. Type 3 collagen is

**Discussion**

Patient 1 was admitted to our hospital two months after the episode of chest pain. Diagnosis of myocardial infarction was obvious on the basis of changes in electrocardiograms and serum enzymes. At the local hospital the electrocardiogram showed ST elevations in leads 2, 3, aVF, and V6 to V5, and at our hospital it showed poor R wave progression and coronary T waves in the precordial leads. The creatine kinase, SGOT and LDH were significantly high. The two-dimensional sector scan of ultrasound disclosed wall motion abnormality and the thallium myocardial perfusion imaging revealed an apical defect. We could not perform cardiac catheterization; therefore, the etiology of myocardial infarction was not known.

Patient 2 was transferred to our hospital on the next day of the episode of chest pain. The changes in electrocardiograms were also compatible with myocardial infarction. On the tenth hospital day it showed pathologic Q waves in leads 1, aVL, and V5 to V6. The creatine kinase and MB fraction were significantly high, and showed serial changes. The two-dimensional sector scan of ultrasound also disclosed wall motion abnormality. The 99m technetium pyrophosphate scintigraphy and thallium myocardial perfusion imaging were also compatible with myocardial infarction. Since patient 2 had blunt trauma to the chest wall, it was possible that he had traumatic contusion to the heart specific therapy; and he was discharged three months later.

**Figure 4.** Characterization of newly synthesized collagen in case 2 was performed as previously described. Briefly, the cultured fibroblasts were incubated with serum-free medium containing 30 μCi of 2,3,4-3H-proline. Collagen was precipitated by five percent trichloroacetic acid from the culture medium. An aliquot was incubated with pepsin at 8°C for 12 h. SDS-polyacrylamide gel electrophoresis was performed according to the method of Laemmli. *Fluorography of the resulting bands was performed for the detection of radioactive bands.* The fibroblasts could not synthesize type 3 collagen (a1 III).
thought to be an essential component of distensible organs such as arteries. Its absence or reduction results in premature wear of such organs with resultant rupture in early adult life. Thus, rupture of large arteries and of the bowel are major catastrophes in this form of Ehlers-Danlos syndrome.\(^5\)\(^6\)

A variety of cardiac abnormalities have been reported in association with Ehlers-Danlos syndrome.\(^3\)\(^4\)\(^7\)\(^8\) Among them are valvular diseases—aortic regurgitation, mitral regurgitation, tricuspid regurgitation, mitral valve prolapse; congenital heart diseases—atrial septal defect, tetralogy of Fallot, dextrocardia; and arrhythmia—complete right bundle branch block, atrioventricular block, and ventricular premature contraction. But myocardial infarction has been very rare. Only one patient with myocardial infarction which seemed to be attributed to this syndrome has previously been reported. He had an aneurysm of the sinus of Valsalva, and his myocardial infarction was likely to have resulted from a hemodynamic problem related to the presence of the aneurysm.\(^19\) No case of myocardial infarction was reported in the type 4 Ehlers-Danlos syndrome. It was most likely that the fragility of coronary arteries due to type 4 Ehlers-Danlos syndrome may have caused myocardial infarction in the present cases.

Finally, cardiac catheterization may be dangerous in type 4 Ehlers-Danlos syndrome, since patient 1 had massive bleeding at the puncture site of the femoral artery and spontaneous rupture of the brachial artery. Thus, cardiac catheterization is not advised for the patient with type 4 Ehlers-Danlos syndrome.

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