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CASE REPORT

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Incidental Myocardial Infarction in Ehlers-Danlos Syndrome Type IV?

ABSTRACT: Ehlers-Danlos Syndrome Type IV is an illness that often leads to premature death due to arterial rupture or dissection and is characterized by very fragile connective tissue. This report documents the death of a 30-year-old man with Ehlers-Danlos Syndrome Type IV from myocardial rupture and cardiac tamponade following a myocardial infarction. We believe that Ehlers-Danlos Syndrome Type IV contributed to the coronary atherosclerosis and myocardial rupture in this young man and that this disease led indirectly to his death by myocardial infarction, an unusual cause of death in this syndrome.

KEYWORDS: forensic science, Ehlers-Danlos Syndrome Type IV, acute myocardial infarction, cardiac tamponade, autopsy, sudden death

Ehlers-Danlos Syndrome type IV is a rare familial disease caused by a mutation in the gene for type III procollagen (COL3A1) (1). This results in either a lack of production of type III procollagen, or production of a defective type III procollagen (2). Production of an abnormal procollagen leads to abnormal formation of collagen fibrils and a decrease in the tensile strength of the tissue. Underproduction of type III procollagen also leads to a decrease in the tensile strength of the tissue.

These molecular defects are manifest as the four diagnostic clinical features of the disease: easy bruising, thin skin with visible veins, characteristic facial features (pinched nose, thin lips, prominent eyes and lobeless ears), and rupture of arteries, uterus, or intestines (1). This clinical picture results from the distribution of type III collagen in arteries and hollow organs.

Unlike other types of Ehlers-Danlos Syndrome, joint hypermobility is not a major feature of the syndrome and skin is thin and translucent rather than hyperelastic (3). The etiology of the skin changes in Ehlers-Danlos Syndrome type IV has been somewhat of a puzzle, as type III collagen makes up only a small component of collagen in the skin. However, it has been shown that normal type III collagen is essential for the formation of type I collagen fibrils (4), the major collagen type in the skin.

The incidence of Ehlers-Danlos Syndrome type IV is unknown, as the minor skin and joint signs often go unreported until the patient presents with a catastrophic bleeding episode. The presence of any of the clinical features above is highly suggestive of a diagnosis, especially in the context of a family history of arterial, intestinal or uterine rupture (5). Diagnosis should be confirmed with a skin biopsy demonstrating the synthesis of abnormal type III procollagen by cultured fibroblasts. The possibility of any haematological disorders also needs to first be ruled out.

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The syndrome displays autosomal dominant inheritance and 50% of offspring from an affected parent will inherit the syndrome. Genetic counseling of parents and also the increased risk of uterine rupture during pregnancy and labour make early diagnosis important in Ehlers-Danlos Syndrome type IV.

Ehlers-Danlos Syndrome type IV often results in premature death, mostly from arterial dissection or rupture, the median survival being 48 years (6). Complications of the disease (arterial, bowel and uterine rupture) arise in approximately 25% of patients by the age of 20 and 80% of patients by the age of 40 (6). Despite the difficulties of surgery in these patients due to very friable tissues and poor wound healing, early intervention may save lives. Regular evaluation by ultrasound and other non-invasive techniques is recommended to detect aneurysms early, and invasive procedures including angiography should be avoided (7). It is important to take seriously any complaint of headache or abdominal pain in a patient with Ehlers-Danlos Syndrome type IV, although the rarity of the disease and its unfamiliarity among physicians may make this problematic.

Case Report

A 30-year-old male, known to have Ehlers-Danlos Syndrome type IV, was found deceased in his car with no suspicious circumstances. The decedent had visited his physician several days prior to his death complaining of severe stomach cramps that he attributed to something he ate. It is unknown whether any treatments or investigations were undertaken with awareness of the decedent's medical condition.

A family history of Ehlers-Danlos Syndrome type IV was evident with the decedent's mother having died at the age of 33 from unknown causes, and his brother died one year before the decedent at the age of 25 from what was described by investigating police as a blood disease (a condition reportedly also affecting the decedent), but assumed to be haemorrhage due to Ehlers-Danlos Syndrome type IV. No information was available on other relatives.

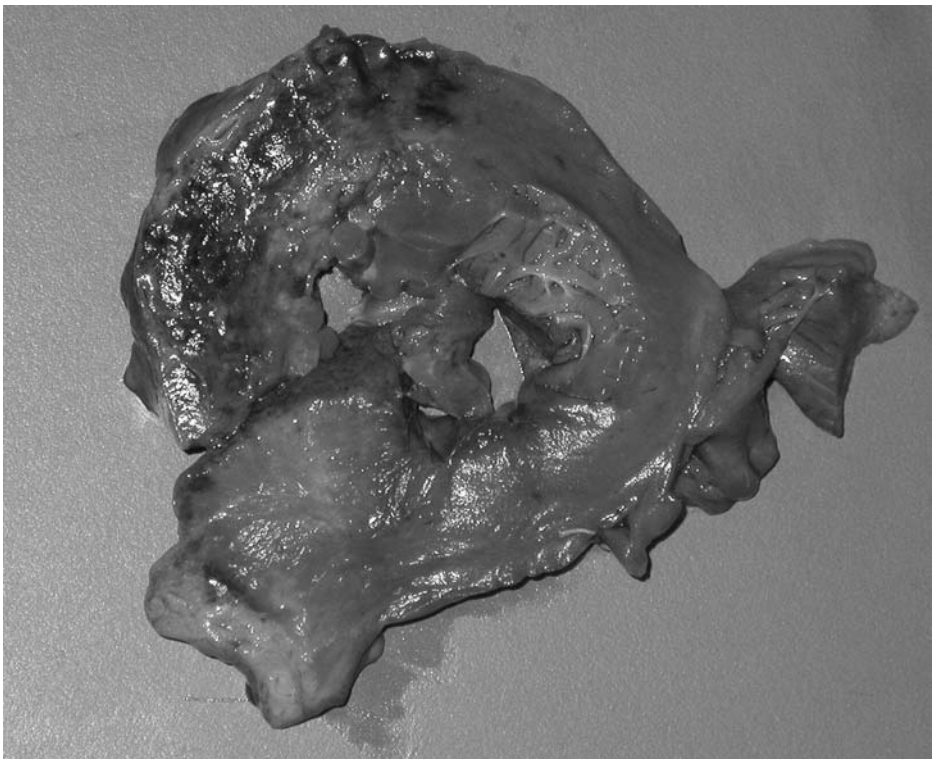

FIG. 1—*Transverse section of left ventricular myocardium showing cardiac rupture and myocardial infarction.*

Autopsy

On external examination, the decedent appeared older than his 30 years and had the typical facies of Ehlers-Danlos Syndrome type IV. The skin was noted to be very thin and translucent with discolouration of the skin of both shins and multiple minor bruises of varying ages elsewhere on the body.

At autopsy, the decedent was found to have a haemopericardium of 900 mL with the resulting cardiac tamponade undoubtedly the cause of death. The source of the haemorrhage was found to be rupture of the free wall of the left ventricle (Fig. 1). Rupture had occurred in an area of myocardial infarction approximately 40mm in diameter involving the lateral and inferior regions of the left ventricular wall. The area of infarction showed some yellow and red discolouration with softening and haemorrhage of the myocardium. These changes would place the age of the infarct somewhere between 3 and 10 days, corresponding with the time the decedent sought medical attention for abdominal cramps, and also the most common time period after an infarct for myocardial rupture (8).

The cause of the myocardial infarction was found to be stenosis of the left anterior descending coronary artery with 70% narrowing of this vessel. Hemorrhage was visible in the vessel wall with the naked eye and was thought to be coronary artery dissection. While spontaneous coronary artery dissection is extremely rare, the phenomenon has been previously reported in Ehlers-Danlos Syndrome type IV (9). On microscopic examination however, no dissection of the left anterior descending artery was found. Stenosis of the vessel was found to be due to coronary atherosclerosis with rupture of the fibro fatty plaque and haemorrhage into the vessel wall (Fig. 2).

The area of myocardial infarction in the free wall of the left ventricle showed infarction of varying ages with some areas exhibiting advanced granulation tissue while other areas showed coagulation necrosis and acute inflammatory changes. The most unexpected finding was the large numbers of myocytes displaying dystrophic calcification, a relatively unusual finding in acute myocardial infarction (Fig. 3).

Findings of mild left ventricular dilatation, diffusely congested lungs, and diffuse nutmeg changes to the liver are all consistent with the cause of death and the preceding myocardial infarction.

A point of interest was the difficulty in suturing the skin after post mortem examination due the extreme fragility of the tissue, a characteristic of Ehlers-Danlos Syndrome Type IV (Fig. 4). Other organs were found to be similarly friable.

Discussion

It seems somewhat unusual that a young man known to have a life shortening condition should die as a result of myocardial infarction unrelated to that condition, when myocardial infarction is comparatively rare at such a young age. It would seem common sense to conclude that the two are somehow linked and that Ehlers-Danlos Syndrome Type IV may have contributed to the progression of coronary artery atherosclerosis and certainly to myocardial rupture.

Myocardial infarction in adults under 45 years is fairly uncommon, making up between 2% and 10% of all myocardial infarctions in the United States (10). Up to 82% of young patients with acute myocardial infarction have typical coronary atherosclerosis, most often single vessel disease (10), and the severity of atherosclerotic changes increases along with the number of risk factors (10). It is not known what risk factors the decedent had, other than that he was not obese and had little evidence of atherosclerotic changes in other vessels. There was no history of stimulant use in this case.

There is the possibility that Ehlers-Danlos Syndrome Type IV may have contributed to the early progression of atherosclerotic

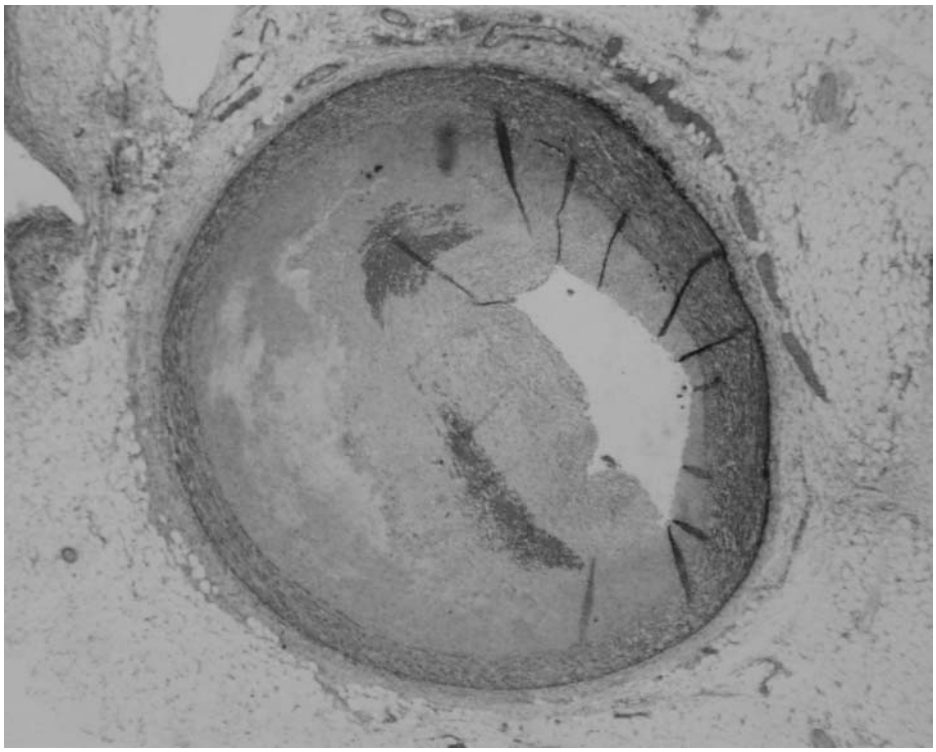

FIG. 2—*Photomicrograph of coronary atherosclerosis with plaque hemorrhage. Movat Pentachrome staining, 1.25× objective).*

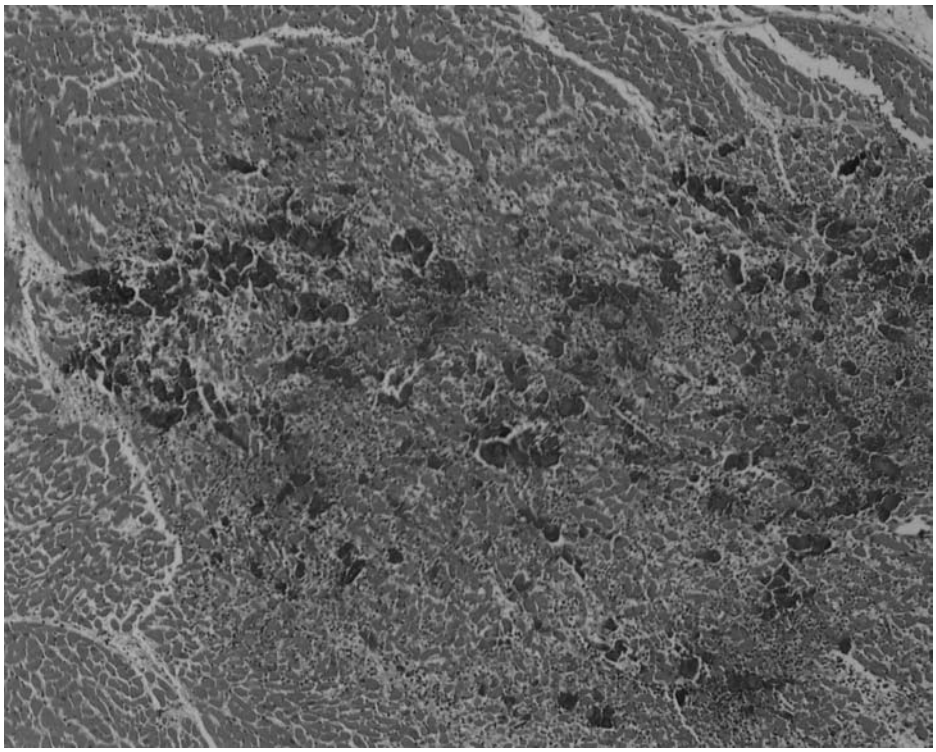

FIG. 3—*Photomicrograph of myocardial ischemic damage with prominent dystrophic calcification. H&E staining, 4× objective).*

changes in the decedent. Native fibrillar collagen has been shown to inhibit smooth muscle cell proliferation in vitro (11), a known step in the process of plaque formation. Does the reduction of normal fibrillar collagen in Ehlers-Danlos Syndrome Type IV leave the path open for smooth muscle cell proliferation in the intima of coronary arteries? Does the lack of normal collagen in the fibrous cap of the plaque more easily dispose to rupture of the plaque?

Likewise, it is possible that Ehlers-Danlos Syndrome Type IV would make an infarcted myocardium more prone to rupture. A decrease in collagen of less than half the normal amount causes

FIG. 4—*Extreme skin fragility in the neck region on restoration of the body following autopsy. Notice the tearing of the skin at the edges of the sutures (arrows), a characteristic feature of Ehlers-Danlos Syndrome Type IV.*

ventricular dilatation and an increase in ventricular compliance (12). Loss of tissue due to infarction in an already compromised myocardium could certainly increase the likelihood of myocardial rupture.

The presence of dystrophic calcification of myocardial cells was an unusual finding. At autopsy there was no evidence of renal failure with both kidneys found to be normal and no evidence of parathyroid disease found. Myocarditis was thought to be unlikely due to sparing of the endocardium, and no other explanation was found. However it has been postulated that calcium influx into the myocardium during infarction may correspond with observed myocyte calcification (13). It is also thought that this calcium influx may be due to high levels of catecholamines and may exacerbate myocyte injury (14).

At first glance this cause of death seems unrelated to the decedent's Ehlers-Danlos Syndrome Type IV, the more typical cause of premature death in this disease being arterial dissection or rupture. However we believe that Ehlers-Danlos Syndrome Type IV has indirectly affected the outcome of an unrelated medical condition resulting in the death of this young man.

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