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【 CASE REPORT 】

Mitral Regurgitation and Heart Failure as the First Presentation in a Patient with Features of Two Connective Tissue Disorders: A Rare Combination of Mucopolysaccharidosis and Osteogenesis Imperfecta?

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Abstract:
Connective tissue disorders sometimes involve cardiovascular systems. This report describes the case of a middle-aged man with mitral regurgitation and heart failure. He had distinctive features of mucopolysaccharidosis type (MPS) III, but no gene mutations that were known to be associated with MPS. Meanwhile, he had a COL1A2 gene mutation that is associated with osteogenesis imperfecta (OI), and had some features that were compatible with OI. The patient might have had a rare connective tissue disorder with the characteristics of MPS III and OI, which was initially detected as a result of the cardiovascular manifestations.

Key words: mucopolysaccharidosis, osteogenesis imperfecta, mitral regurgitation, heart failure

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Introduction

Connective tissue disorders manifest with a wide range of clinical findings, and the manifestation varies according to the type of disorder. Cardiovascular involvement sometimes occurs, and is a major cause of death in patients with these disorders. We herein describe the case of a patient with a rare connective tissue disorder that might have been a combination of mucopolysaccharidosis type (MPS) III and osteogenesis imperfecta (OI), in whom the initial manifestations were mitral regurgitation and heart failure.

Case Report

A 53-year-old man was admitted to our hospital to undergo treatment for mitral regurgitation and heart failure. He was born following an uneventful pregnancy with a normal birth weight. He had no specific family history. Until 51 years of age, he had lived with his parents and had not been diagnosed with any specific disease. He developed dyspnea on exertion, and had been diagnosed as having congestive heart failure and mitral regurgitation two years previously. He had repeated episodes of worsening heart failure, despite medication, and was referred to our hospital to undergo further investigation for mitral regurgitation and heart failure.

On admission to our hospital, his height was 140 cm and his weight was 35.9 kg. He had coarse facial features, macrocephaly, and an inguinal hernia. Chest X-ray showed thoracic compression fractures and scoliosis. The patient's bone density was markedly decreased. Chest X-ray also showed severe cardiomegaly with a cardiothoracic ratio of 75% (Fig. 1A and B). An electrocardiogram demonstrated atrial fibrillation with poor R wave progression in the precordial

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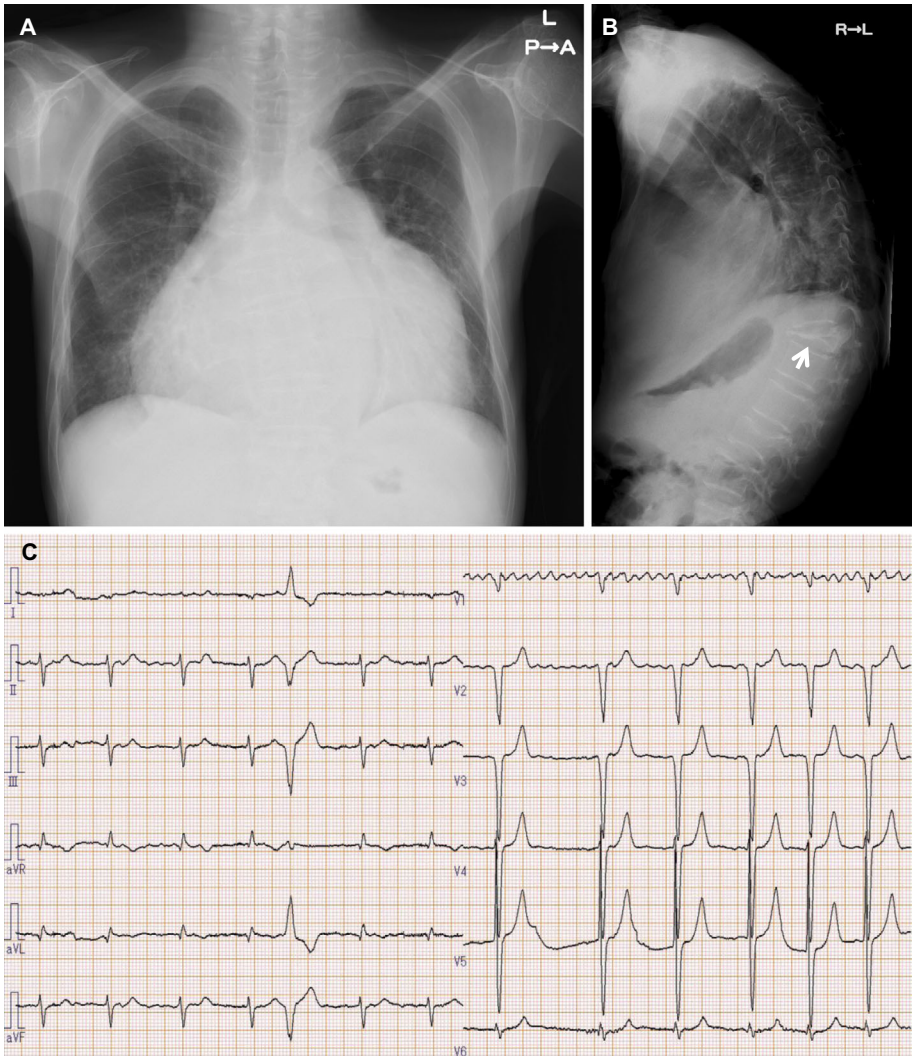

Figure 1. **Chest X-ray and electrocardiography. A: Frontal view. Severe cardiomegaly was noted. B: Lateral view. Chest X-ray demonstrated a compression fracture (white arrow). C: Electrocardiography revealed atrial fibrillation, premature ventricular contraction, and poor R wave progression in the precordial leads.**

leads (Fig. 1C). The patient's brain natriuretic peptide level was elevated to 902 pg/mL. Transthoracic echocardiography revealed moderate degenerative mitral regurgitation with a myxomatous appearance and redundant valve tissue. The size and ejection fraction of the left ventricle were normal (left ventricular dimension in diastole, 49 mm; left ventricular ejection fraction, 60%). The Interventricular septum and posterior wall thicknesses were both 10 mm. The left atrium was severely dilated (left atrial diameter, 65 mm; left atrial volume index, 227 mL/m^2) (Fig. 2). The mitral inflow was restrictive (deceleration time, 114 ms). After the optimization of the patient's medications, cardiac catheterization demonstrated moderate mitral regurgitation (Grade II), compensated hemodynamics, and no significant coronary artery stenosis. Based on the results of echocardiography and cardiac catheterization, we concluded that the degree of mitral regurgitation was moderate, and surgery was not indicated. Cardiac magnetic resonance imaging and ^{18}F-fluorodeoxyglucose-Positron emission tomography revealed no specific inflammatory and/or infiltrative cardiomyopathy. Although the precise etiology remained unknown, his heart failure might have been caused by diastolic dysfunction (based on the restrictive pattern of mitral inflow and the severely dilated left atrium). Atrial fibrillation and/or moderate mitral regurgitation might have affected his heart failure to some extent. Thus, we continued to provide medical treatment for his heart failure.

On the other hand, we suspected some kind of hereditary disorder as an underlying etiology, because of his short stature, characteristic facial features, macrocephaly, juvenile compression fractures, inguinal hernia, and mental retardation. The levels of vitamins, and thyroid, parathyroid, and pituitary hormones were within the normal ranges. Among the congenital metabolic disorders, we considered - based on his features - that there was less possibility of his disease being a mitochondrial disease or glycogenosis. We suspected MPS, and examined the urine uronic acid excretion. This showed an increase in urine uronic acid excretion (15.2 mg/

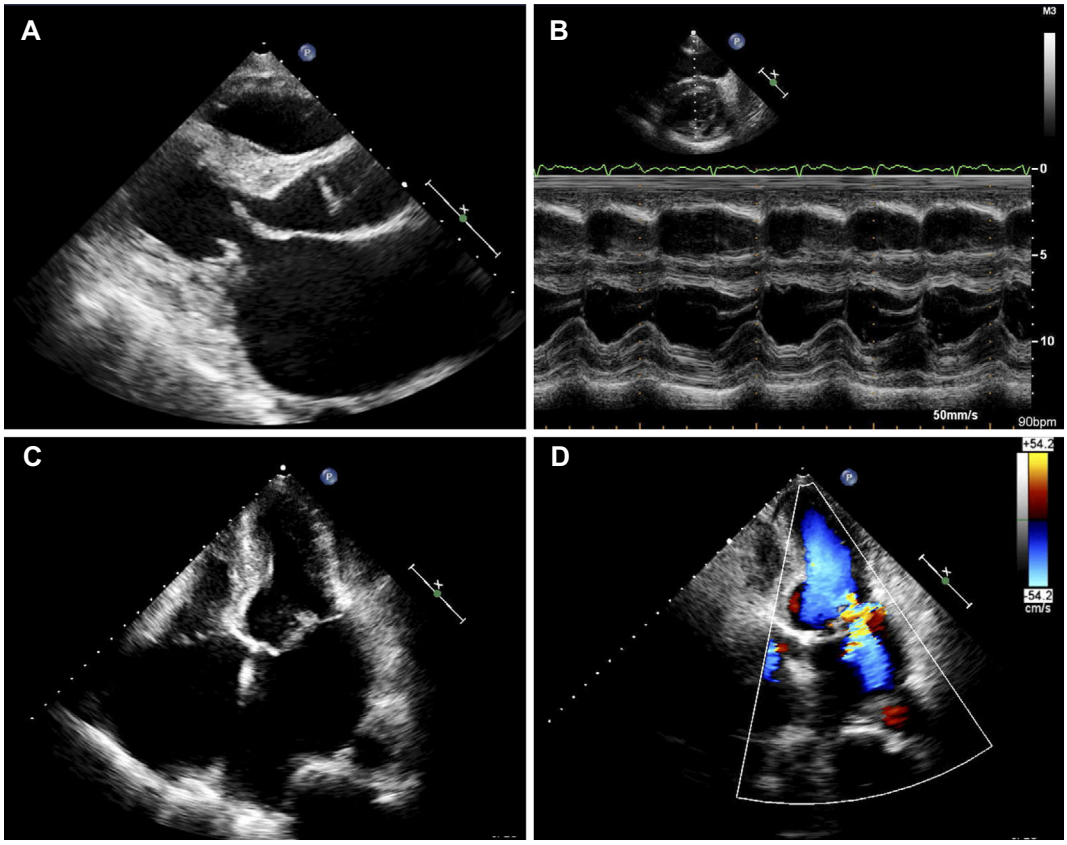

Figure 2. **Transthoracic echocardiography. A: The parasternal long axis view. Mild concentric hypertrophy of the left ventricle was noted. B: M-mode echocardiography. The size and ejection fraction of the left ventricle were normal. C: Apical four-chamber view. The redundant mitral valve and a severely dilated left atrium were noted. D: The degree of mitral regurgitation was moderate.**

g creatinine), especially in the fraction of heparan sulfate. The heparan-N-sulfatase activity was decreased to 15.6 nmol/mg protein/17 hours (normal range: 18.8 to 58.1 nmol/mg protein/17 hours) in the white blood cells. Thus, MPS III was suspected, although the enzyme activity was relatively close to the normal range for MPS III patients. We planned and performed genetic screening for MPS III. In parallel, we also screened for other genes (that were available at our hospital).

While the patient was undergoing genetic screening, his condition became complicated by an urinary tract infection, recurrent pneumonia and heart failure, and he died of sepsis. An autopsy was performed with the consent of his family.

Pathological analysis

On autopsy, the anterior mediastinum showed jelly-like myxomatous degeneration and foam-like changes of the connective tissues. The heart was enlarged with concentric hypertrophy (Fig. 3A), and the heart weight was 500 g (heart to body weight ratio: 1.4%). The heart and epicardium also showed jelly-like myxomatous degeneration. All of the valves showed thickening, and the mitral valve was degenerated and the bileaflets were billowing; as shown in Fig. 3B. A microscopic examination showed fibrotic thickening and myxomatous change in the mitral valve. Alcian blue staining revealed acid mucopolysaccharide accumulation, and electron microscopic examination demonstrated mucopolysaccharide in the lysosomes of interstitial cells. Meanwhile, Masson's trichrome staining showed kinked and relatively few clumps of collagen fibers (Fig. 4). The accumulation of acid mucopolysaccharide and relatively few clumps of collagen fibers were also noted in the interstitium of the myocardium (Fig. 5). Chronic thoracic aortic dissection (to a limited extent) was noted, and relatively few clumps of kinking collagen fibers were observed in the aorta (Fig. 6A). The presence of plump clear cells was seen in the coronary artery intima and media. The elastic fibers in the coronary arteries showed disruption and fragmentation (Fig. 6B and C). The same findings were also seen in the cerebral, hepatic, renal, and pulmonary arteries. Hepatosplenomegaly was not seen; the liver was atrophic (weight 698 g), and the spleen weight was 125 g. The cranial bone was thick and solid. Meanwhile, the vertebrae and ribs were fragile. The cerebral white matter showed multiple disseminated areas of demyelination.

Genetic analysis

Although MPS III was the mostly highly suspected diag-

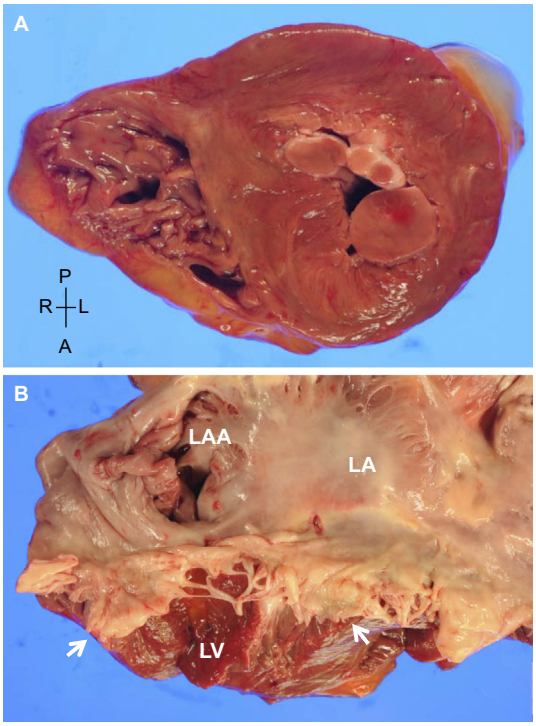

Figure 3. **The macroscopic appearance of the heart and valves. A: Heart. Concentric hypertrophy of the myocardium was noted. B: Mitral valve. Both the anterior and posterior leaflets were thickened (white arrow). A: anterior, L: left, LA: left atrium, LAA: left atrial appendage, LV: left ventricle, P: posterior, R: right**

nosis in this case, exome sequencing did not reveal any gene mutations known to be related to MPS type IIIA, IIIB, IIIC, or IIID (SGSH, NAGLU, HGSNAT, and GNS genes, respectively). Meanwhile, we identified a mutation of the COL1A2 gene that is known to be associated with OI. Exome sequencing led to the identification of a mutation consisting of NM_000089.3(COL1A2):c.4048G>A (p.Gly1350Ser).

Discussion

Although exome sequencing revealed no known MPS III gene mutations, our case had distinctive features of MPS III. He also had a COL1A2 gene mutation associated with OI and had some features that were compatible with OI (Fig. 7).

MPSs are lysosomal storage disorders, which are characterized by the deficiency of enzymes that act in the sequential catabolism of glycosaminoglycans (GAG). Individuals with these rare disorders are affected by the progressive accumulation of incompletely degraded GAG within virtually all organ systems; however, the distribution varies depending on the disease (1). The diagnosis and type of MPS are defined by the determination of the urinary excretion of the corresponding GAG and the missing enzyme activity (2). Numerous gene mutations have been identified within each gene responsible for the specific types of MPS; however, much remains unknown.

The typical manifestations of MPS include growth retardation, skeletal deformities, dysmorphic facial characteristics, central nervous system involvement, inguinal hernia, hepatosplenomegaly, and ocular and hearing impairment. Cardiac involvement has also been reported in all MPS syndromes; however, it is a common feature of those with MPS type I, II, and VI (3). Cardiac valve thickening and dysfunction, and cardiac muscle hypertrophy are commonly present. In our case, the pathological analysis demonstrated the accumulation of acid mucopolysaccharides in the valves, especially in the lysosomes of the interstitial cells, and in the interstitium of the myocardium, strongly suggesting the patient was complicated with MPS. With regard to the coronary artery pathology, a recent report showed that coronary artery involvement could occur in some types of MPS; however, the precise mechanisms are not yet known based upon our understanding of GAG pathobiology. In our case, we identified vacuolar degeneration in the intima and media of the coronary arteries, which was consistent with a previous report (4). A number of findings were observed that were characteristic of MPS: increased metabolic products in the urine, decreased enzyme activity, albeit mild, and the accumulation of mucopolysaccarides in various tissues. Although we did not identify any specific gene mutations that are known to be associated with MPS III, it is possible that intronic or other mutations were present that could not be detected by exome sequencing. In view of the diversity of the MPS types, it is possible that the patient might represent a new type of MPS.

In addition to the features suggesting MPS III, we found that the patient had a COL1A2 gene mutation. The COL1A2 gene encodes the chains for type I collagen, and mutations in this gene are associated with OI. There are no diagnostic criteria for OI, and its clinical diagnosis depends on the presence of a number of features. The common clinical manifestations include bone fragility resulting in fractures, deformity, bone pain, and immobility. Blue sclera, conductive hearing loss, dental abnormalities, and inguinal hernia are typical extraskeletal manifestations (5). OI patients sometimes have cardiovascular abnormalities because type I collagen is a major component extracellular matrix of the cardiac and aortic wall. A decrease in the amount of fibrotic connective tissue in the valves can occur, resulting in severe valvular regurgitation in some cases of OI (6). Cardiac dysfunction and/or aortic dissection can also occur in patients with OI (7). In our case, the patient's short stature, bone fragility, inguinal hernia, and cardiovascular involvement, including mitral regurgitation, recurrent heart failure, and aortic dissection, could be explained by OI. The pathological analysis revealed kinked and relatively few clumps of collagen fibers in the myocardial interstitium, valves, and the aorta; findings which are compatible with the pathological features of OI (8, 9). However, there was no evidence of blue sclera, hearing loss, or dental abnormalities. In addition, the patient's mutation is considered to be a rare vari-

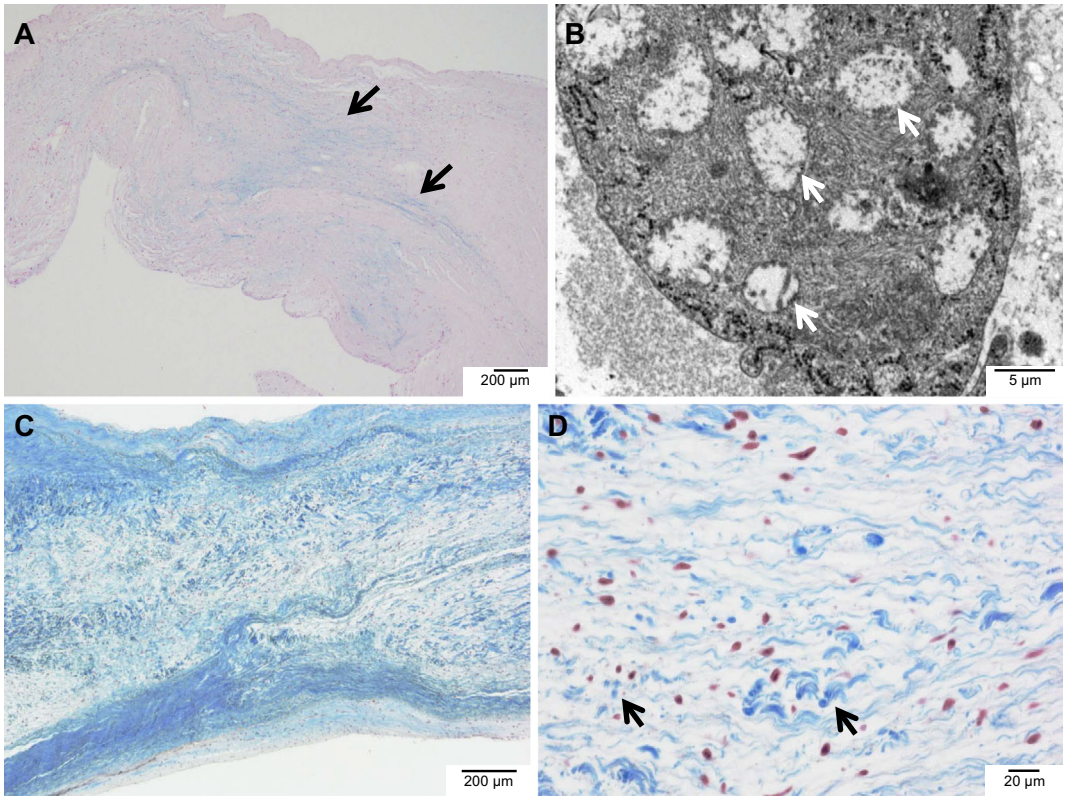

Figure 4. **The microscopic analysis of the mitral valve. A: Acid mucopolysaccharide accumulation (black arrow) was identified (Alcian blue staining). B: Mucopolysaccharide accumulation (white arrow) was seen in the lysosomes of the interstitial cells in the mitral valve (Electron microscopy). C: The mitral valve (Masson's trichrome staining). D: Masson's trichrome staining revealed kinked and relatively few clumps of collagen fibers in the mitral valve (black arrow).**

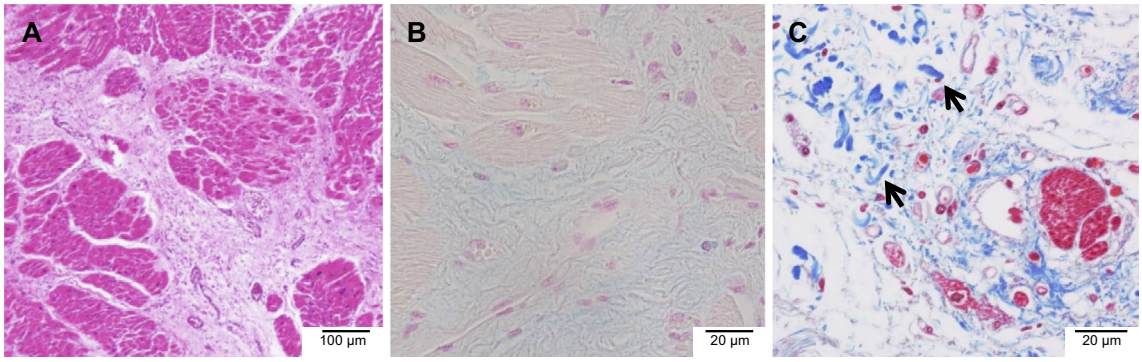

Figure 5. **The microscopic analysis of the myocardium. A: Myocardial cell atrophy and mucinous accumulation in the interstitial tissue were noted (Hematoxylin and Eosin staining). B: Acid mucopolysaccharide accumulation was identified in the myocardial interstitium (Alcian blue staining). C: Kinked and relatively few clumps of collagen fibers were noted (black arrow) (Masson's trichrome staining).**

ation among OI patients (10), and occurs in the C-terminal domain. Thus, the association between the patient's COL1A2 gene mutation and his clinical features is unclear. Furthermore, the increased urine metabolic product excretion, enzyme activity abnormality, and mental retardation could not be explained by OI alone. It is possible that the patient might have had a rare, unusual, unknown connective tissue disorder, with the characteristics of two rare diseases, MPS and OI; however, this is mere speculation.

In conclusion, this case was considered to involve a relatively rare type connective tissue disorder, in which the initial presentation was heart failure and mitral regurgitation; however, a definite diagnosis could not be made. Cardiologists should bear in mind the possibility of connective tissue

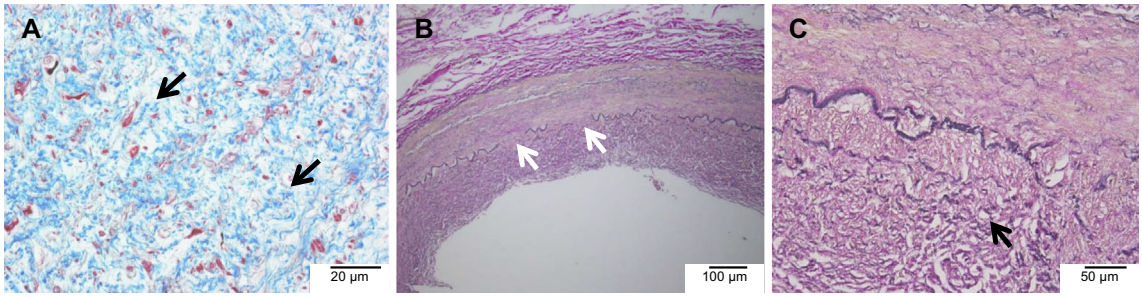

Figure 6. **The microscopic analysis of the aorta and coronary artery. A: Kinked and relatively few clumps of collagen fibers in the aorta (black arrow) (Masson's trichrome staining). B: The elastic fibers were disrupted and fragmented (white arrow) in the coronary artery (Elastica van Gieson staining). C: Clear cells were present within the coronary artery intima (black arrow).**

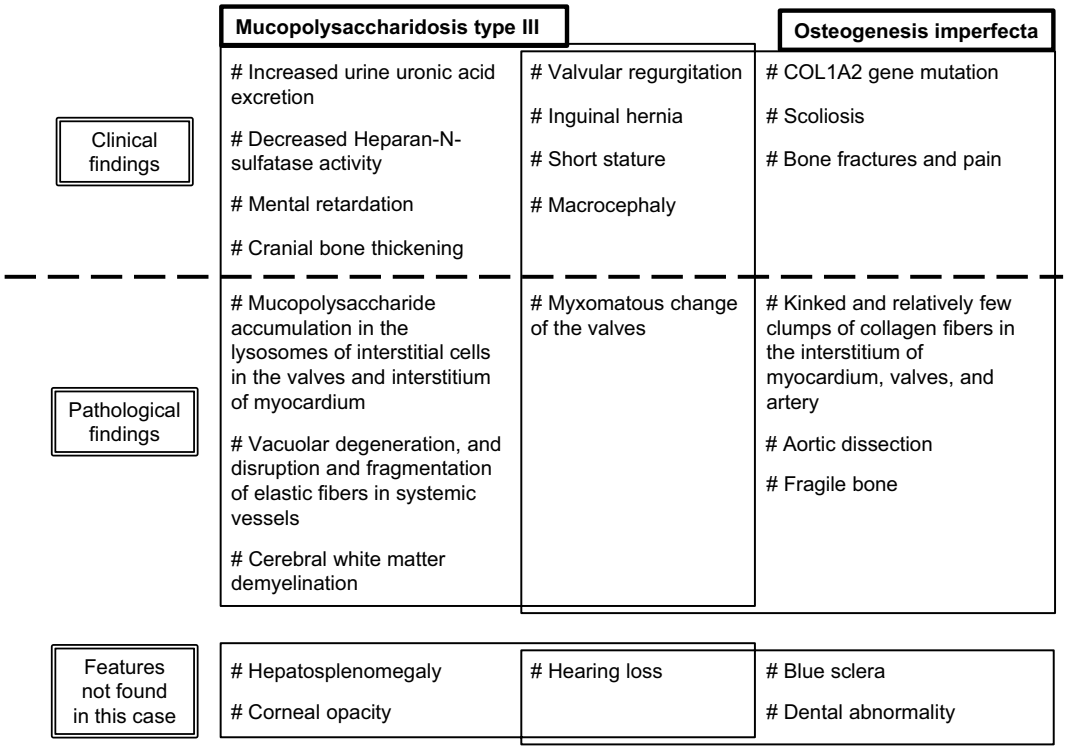

Figure 7. **A summary of the findings in the present case.**

disorders in their medical practice, when patients with cardiovascular disease show characteristic features.

The authors state that they have no Conflict of Interest (COI).

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