CASE REPORT

Dilated aortic root and severe aortic regurgitation causing dilated cardiomyopathy in classic Ehlers-Danlos syndrome

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SUMMARY

Ehlers-Danlos syndrome (EDS) is a group of heritable disorders characterised by vast clinical heterogeneity ranging from the classic constellation of symptoms including skin hyperextensibility, joint hypermobility and skin fragility to the exceedingly critical consequences of arterial rupture and visceral perforation. We describe the case of a 65-year-old male with a history of classic EDS who reported of dyspnoea on exertion, orthopnoea, fatigue and palpitations. He was found to have dilated cardiomyopathy with an ejection fraction of 35%, aortic root dilation and severe aortic valve regurgitation. The authors intend to draw attention to the rare cardiac manifestations of this condition and the therapeutic challenges involved in managing such patients.

long described but its exact management strategies are not well defined.^{5 6} We report a challenging case of aortic root dilation, severe aortic regurgitation and severe dilated cardiomyopathy in a patient with EDS of the classic type.

CASE PRESENTATION

A 65-year-old man with a history of gastrointestinal reflux disease and skin biopsy proven classic EDS presented to the cardiology outpatient department reporting of dyspnoea on exertion, orthopnoea, fatigue and palpitations. The patient had a family history significant for EDS, in which his father and elder brother died suddenly in their 40s. Consequently, our patient and his younger sibling underwent genetic testing in their 30s to rule out other more common causes of sudden cardiac death including hypertrophic obstructive cardiomyopathy and prolonged QT syndromes. It was then that other diagnoses were excluded and he was found to have a mutation of the COL5A1 gene that was consistent with classic EDS. He reported of progressive worsening dyspnoea on exertion for 2 months and two-pillow orthopnoea. His only medication was pantoprazole 40 mg daily. He had never smoked tobacco and does not drink any alcohol. His vital signs were significant for a blood pressure of 145/50 mm Hg and a heart rate of 80 bpm. Physical examination revealed lax extensible velvety skin and hypermobile joints (figure 1). His cardiovascular examination revealed a laterally displaced apex beat, normal jugular venous pressure, S3 gallop and a 3/6 intensity diastolic murmur heard loudest at the left sternal border. Respiratory auscultation revealed mild bibasilar crackles without any wheeze and he did not have any pitting pedal oedema.

BACKGROUND

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disorder affecting collagen production, processing and structure.¹ It is a rare condition with a prevalence estimated at ~1 in 5000.² The Villefranche classification scheme for EDS recognises six subtypes that are based on clinical, biochemical and genetic findings.² The subtypes are as follows: classic, hypermobility, vascular, kyphoscoliosis, arthrochalasia and dermatosparaxis. The classic, hypermobility and vascular subtypes are the most common, while the other subtypes are much rarer.³ Approximately 50% of patients with a clinical diagnosis of classic EDS experience mutations in the COL5A1 and COL5A2 gene.⁴ The majority of patients have a non-functional COL5A1 allele resulting in insufficient type V collagen. A smaller percentage of patients have a mutation in COL5A1 or COL5A2, leading to a functionally defective type V collagen.⁴ The cardiovascular manifestations of EDS have been

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Figure 1 Hypermobile joints (left) and hyperextensible velvety skin (right).

Figure 2 Chest X-ray revealing marked cardiomegaly.

Initial laboratory investigations including haematological, biochemical and coagulation studies were within normal limits, however, brain natriuretic peptide was elevated at 590 pg/mL (normal <100 pg/mL). His chest X-ray revealed marked cardiomegaly without any overt pulmonary oedema (figure 2). His ECG revealed left bundle branch block with a heart rate of 75 bpm with frequent premature ventricular complexes in a pattern of bigeminy and poor R-wave progression (figure 3). A 24-hour holter monitor revealed premature ventricular complexes and no other abnormalities. A transthoracic echocardiogram (TTE) showed a significantly dilated left ventricle measuring an end diastolic diameter of 10 cm, (figure 4) with an ejection fraction (EF) of 35%, aortic root dilation (4.9 cm) and severe aortic valve regurgitation (AVR) (figure 5). Owing to the presence of vascular and cardiac complications, which are not ordinarily associated with classic EDS, an aortic panel sequencing of 21 genes was carried out in our centre to rule out other causes for familial aortopathy. The results reconfirmed classic EDS associated with COL5A1 gene mutation and therefore other causes were excluded. A cardiac biopsy was considered but was deferred given the likely diagnosis of EDS associated aortopathy. The patient was treated with oral furosemide 40 mg daily, carvedilol 3.25 mg twice daily and lisinopril 10 mg daily. The patient had a dramatic improvement of his

Figure 4 Echocardiogram showing significant left ventricular dilation (end diastolic diameter of 10 cm).

symptoms within days and was closely followed in the outpatient office. A subsequent CT scan of the chest with contrast confirmed an aortic root dilation of 4.9 cm. A coronary angiogram revealed non-obstructive mild coronary artery disease. After the procedure, the patient developed a pseudo aneurysm of the right femoral artery at the puncture site, which was successfully treated with thrombin injection.

The patient was referred for specialist cardiothoracic surgery evaluation in view for aortic root and valve replacement. The patient was deemed to be high risk for surgery because of his EDS with a surgical mortality risk above 10%. The patient was offered surgical intervention but declined. He opted for medical management that included a diuretic, a β -blocker and an ACE-inhibitor.

OUTCOME AND FOLLOW-UP

The patient remained essentially asymptomatic for 9 months during his outpatient follow-up appointments. His condition began to deteriorate thereafter and he required multiple hospital admissions for congestive heart failure. A repeat TTE at 12 months showed worsening degree of AVR and left ventricular EF of 20%. He subsequently died of cardiopulmonary arrest during his fourth hospitalisation, which was thought to be

Figure 3 ECG showing left bundle branch block with a heart rate of 75 bpm with frequent premature ventricular contractions in a pattern of bigeminy and poor R-wave progression.

Figure 5 Echocardiogram showing dilated aortic root measuring 4.9 cm with severe aortic regurgitation.

secondary to flash pulmonary oedema. Unfortunately, attempts at cardiac resuscitation did not succeed and he died with pulseless electrical activity cardiac arrest.

DISCUSSION

This case report describes a patient with significant cardiac manifestations with the classic type of EDS. Interestingly, advanced cardiovascular involvement tends to occur more commonly in the vascular subtype (type IV) rather than the classic subtype, however, clinical overlap does exist.⁷ Despite that, varying frequencies of cardiovascular complications of the classic subtype have been reported in the literature including mitral valve prolapse, mild systolic and diastolic dysfunction, aortic and tricuspid regurgitation, dilated aortic root and cardiovascular dysautonomia.^{5 6 8 9}

In the classic type of EDS, the literature for the most part supports a relatively benign course of cardiac involvement and the lifespan of patients is usually comparable to the general population. In one study of classic patients with EDS, the incidence of aortic root dilation was 33%.¹⁰ In another study of 38 patients with classic and hypermobile EDS, 13% of patients had significant dilation of the aortic root, 30% had impaired left ventricular relaxation and only two patients had mild left ventricular systolic dysfunction.⁹ Although the onset of aortic root involvement appears to begin as early as childhood, the rate of progression and its consequences are exceedingly varied.

The advanced degree of severe left ventricular dysfunction seen in our patient is a manifestation of long-standing aortic root dilation and aortic regurgitation. This degree of cardiac dysfunction is uncommon in classic EDS. Most of these patients with structural cardiac abnormalities will only need active surveillance. If no abnormalities are found on the initial echocardiogram in an adult with EDS, a follow-up echocardiogram is not routinely required; however, prospective studies on the progression of aortic dilation in such individuals have not been carried out. If an abnormality is discovered, follow-up echocardiogram is recommended on a yearly basis.⁴ A small, but unknown percentage requires symptomatic medical treatment and rarely surgical intervention. Unfortunately, the friable nature of tissues and vasculature in this subgroup of patients means that surgical intervention poses a high risk of bleeding, false aneurysms and death.

Evidently, scientific literature is limited when it comes to reporting the number of surgical procedures carried out in this patient population, particularly when vascular structures are involved. Aortic valve replacement secondary to aortic stenosis

has been reported in classic EDS; however, vascular biopsy in this successful case reported no abnormality in the collagen architecture, which was a definite advantage.¹¹ Optimistically, a handful of case reports of successful elective and emergency surgeries involving the thoracic aorta, the aortic valve and the coronary arteries have been reported where vascular involvement existed.^{11–14}

Although our patient was diagnosed with the classic EDS subtype, he was undoubtedly considered higher risk and rather unexpectedly comparable to the more precarious vascular subtype of EDS evident by his coronary angiogram complicated by a pseudo aneurysm. While this case was managed well, there were certain limitations. This patient would have benefited from a cardiac biopsy and/or aortic biopsy for definitive tissue evaluation. The family declined an autopsy due to religious reasons and although this does not change the outcomes of this case, it may have provided a missed diagnosis that could have guided the management for future family members.

It is difficult to determine whether our patient would have benefited from surgical intervention, however, the consequence of not intervening was catastrophic. Accordingly, we reiterate the importance of approaching the notion of invasive surgical intervention with caution in EDS and we urge early specialist surgical referral as surgery can have the potential for improving mortality.

Learning points

- ▶ Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disorder affecting collagen production, processing and structure.
- ▶ Cardiovascular involvement tends to occur more commonly in the vascular subtype (type IV) rather than the classical subtype.
- ▶ Cardiovascular complications of the classic subtype include mitral valve prolapse, mild systolic and diastolic dysfunction, aortic and tricuspid regurgitation, dilated aortic root and cardiovascular dysautonomia.
- ▶ Surgical intervention should be taken with caution in patients with EDS and early specialist surgical referral is vital.

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