Brief Communication

The Role of Connective Tissue Genomics in Ascending Aortic Dissection: A Marfan Syndrome Scenario

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Abstract

Background: Aortic dissection is a rare yet life threating condition with some already discovered risk factors namely hypertension, connective tissue disorders such as Marfan syndrome (MFS), cocaine abuse and cigarette smoking.

Case report: In this article we would like to present a case of MFS who presented with severe chest pain and undergone Bentall surgery due to aortic dissection and aneurysm.

Conclusion: Although many risk factors and preventive measures are already investigated, there is no definite method to avoid its occurrence in genetically predisposed patients such as MFS. Patient-specific models utilizing embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) may offer some advantages.

Keywords: Aortic Dissection, Marfan Syndrome, Induced Pluripotent Stem Cell; Embryonic Stem Cell

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Introduction

Acute aortic dissection is a rare yet life-threatening condition, arising from a tear in the aortic intima and entering blood into the medial layer of the aorta. This will lead to a progressive separation of the aortic wall layers and formation of a false lumen which is susceptible to rupture (1).

Several risk factors are proved to be associated with the development of clinical aortic dissection, which can be categorized into two main groups; factors resulting in medial degeneration like Marfan syndrome and those increasing aortic stress wall, most important of which being hypertension (1, 2).

Marfan syndrome (MFS), a rare autosomal dominant connective tissue disorder, mostly occurring as a result of mutations in the FBN1 gene, located on chromosome 15q21.1, which is in charge of encoding fibrillin-1 (3, 4). Aortic dissection is among the cardiovascular manifestations of Marfan syndrome which is the main cause of death in such patients. MFS is a pleiotropic disease with complete penetrance yet highly variable phenotype affecting ophthalmologic, musculoskeletal, cardiovascular and pulmonary systems, which indeed necessitates individual clinical and genetic workup (3-5).

Fibrillin-1, a glycoprotein, is among the foremost components of microfibrils, hence playing an important role in the structure of the extracellular matrix. Thus, any qualitative or quantitative

alterations in this protein as can be seen in MFS leads to tissue fragmentation and degeneration, increased TGF-β and abnormal interactions in cell-matrix (6).

In the last decades, gene-editing technologies have drawn attention using embryogenic stem cells (ESC) and induced pluripotent stem cells (iPSC). ESC and iPSC offer the advantage of being patient-specific and may help reveal all aspects of the disease and help in to discover appropriate treatment (7-9).

Cocaine, on the other hand, is another risk factor for developing aortic dissection (1, 10). It is assumed that cocaine abuse may lead to the release of catecholamines, thus raising the blood pressure and increasing the wall stress of aorta (10-12). Smoking is another potential risk factor that accounted for aortic dissection progression; its effect is contributed to vasoconstriction and elevation of TGF-B (13).

Case Report

A 29-year-old male was admitted to the emergency department due to severe chest pain. He complained of new-onset sharp retrosternal pain radiating to the left shoulder which started a few hours before admission and worsened with activity. The patient had disproportionately long and slim extrimities with long fingers and toes as well as sternum deformity. He was slim and approximately two meters high. All of these evidences suggested previously undiagnosed Marfan syndrome. In addition, he was not only a smoker but also had a history of addiction to various kinds of drugs such as opium, cocaine, amphetamines, etc.

During workup, CT angiography revealed aortic dissection initiating at aortic root extending to the iliac artery bifurcation. Bedside echocardiography also demonstrated an ejection fraction of 50% with mild to moderate mitral regurgitation, free AI and Aortic Aneurysm.

The patient was soon transferred to the operating room for emergency cardiac surgery. After preparing full cardiac monitoring including 3 lead electrocardiogram, pulse oximetry, non-invasive blood pressure, invasive blood monitoring via left radial artery and cerebral oximetry following by preoxygenation, patient was anesthetized with 2 mg Midazolam, 100µg Fentanyl and 20 mg Etomidate, neuromuscular blockade was achieved with Pancuronium. After endotracheal intubation, right internal Jugular vein was cannulated for central venous access and two large bore (14G) intravenous access was placed. Then Foley catheter was fixed in able to urine output.

After prep and drape, the surgery had initiated by exploring the left femoral artery and cannulating it after administration of Heparin. Afterward sternotomy was performed. Brachiocephalic artery and left carotid artery were also cannulated before initiating cardiopulmonary bypass and pericardiotomy. The ascending aorta was both dissected and aneurysmal. Aneurysm involved the aortic arch; however, dissection was extended to both iliac arteries and left femoral artery (Figure 1). The surgeons decided to perform Bentall surgery. Therefore, aortic valve, aortic root and ascending aorta were all removed and replaced by the mechanical aortic valve and composite tube graft. Then coronary arteries were implanted into the newly placed graft (Figure 2). Afterward competency of replaced aortic valve was confirmed with transesophageal echocardiography and patient was weaned from cardiopulmonary bypass. Nevertheless, hemostasis was not adequate enough to completely close the sternum. Finally, the patient was transferred to intensive care unit for postoperative care. Patient's hemodynamic was stable during surgery and afterwards. Sternum closure was done the day after. He was weaned from mechanical ventilation after few days and was discharged with good condition after ten days.

Definite diagnosis of Marfan syndrome based on Ghent criteria was made after the complete stabilization of the patient.

Intraoperative TEE was done without complication as well as postoperative TEE after six days, results are as below:

Intraoperative TEE:

- Mild left ventricular (LV) enlargement with mild LV systolic dysfunction and left ventricular ejection fraction equivalent to 45%
- Tricuspid aortic valve with severe aortic insufficiency
- Annuloaortic ectasia with the aortic annulus of 33 mm

- Aneurysmal aortic root and ascending aorta

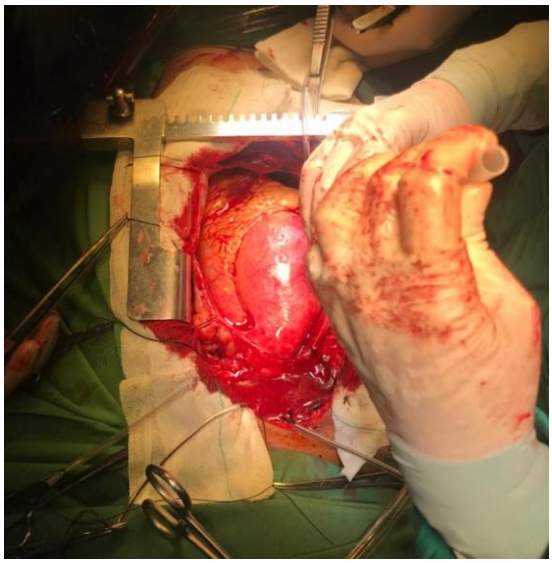

Figure 1. The figure shows dilated ascending Aorta and aortic arch before being replaced

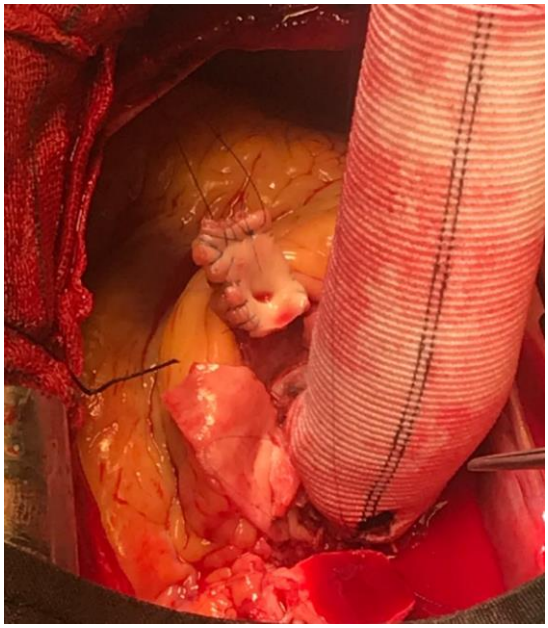

Figure 2. This figure indicates placement of composite tube graft after aortic valve replacement during Bentall surgery

- Prolapse of AMVL and PMVL with up to moderate MR
- Type A dissection, the intimal flap was seen superior to ST junction
- -Postoperative TEE (after 6 days)
- Mild LV enlargement and moderate LV systolic dysfunction with The LVEF estimated to be approximately 35%
- Global hypokinesia
- Grade 2 diastolic dysfunction
- Well seated and functional mechanical aortic valve
- The aortic graft was seen with no abnormality
- Intimal flap in the aortic arch and descending

aorta with extension to the left carotid artery

- Presence of intimal flap in the abdominal aorta

Discussion

Acute aortic dissection is an infrequent yet life-threatening condition and if left untreated it has a mortality rate of 1-2% per hour (1). Clinical presentation usually imitates myocardial infarction or pulmonary embolism (1). Therefore, it is necessary to be aware of risk factors in order to diagnose such a condition, thus initiating the treatment as soon as possible.

Several risk factors are described in the literature, namely, advanced age, male gender, history of hypertension, use of cocaine, being smoker, some connective tissue disorders such as Marfan syndrome or Ehlers Danlos syndrome, presence of aortic aneurysm or bicuspid Aortic valve (2).

MFS is a hereditary disorder as a result of FBN1 mutation, encoding the extracellular matrix protein fibrillin-1. As a result, microfibril structures will degenerate and ECM integrity of aortic tunica media will be lost, making it prone to dissection (14).

The aforementioned mutation also leads to increased angiotensin 2 receptors signaling and subsequent increase in TGF-B which results in altered hyaluronan synthesis, increased apoptosis, and impaired CD-34 positive progenitor cell recruitment. Consequently, the aortic wall becomes fragile and susceptible to tearing.

Increasing microRNA-29b has a principal role in MFS pathogenesis, by altering normal aortic wall apoptosis and extracellular matrix structure (14, 15, 16). On the other hand, cocaine abuse is a well-known predisposing factor for developing aortic dissection, especially in the patient who suffers from chronic hypertension. It acts both centrally and peripherally by inhibiting reuptake of catecholamines namely epinephrine, norepinephrine and dopamine, thus increasing overall catecholamine release, which in turn leads to sympathetic activation and an abrupt increase in blood pressure, heart rate and cardiac contractility. Hence it can be concluded that such fulminant hypertension especially if coinciding with other risk factors may lead to dissection of the aorta (11, 12). Interestingly in a study by Henning LD et al, Cocaethylene which is produced as a metabolite of simultaneous consumption of ethanol and cocaine decreased myocardial contractility and stroke volume which suggested a protective effect against dissection formation (17).

The last known risk factor in the current case is cigarette smoking. It is assumed that smoking enhances the vasoconstriction associated with cocaine abuse. Moreover, smoking also affects vascular structure by increasing TGF-B (13).

In conclusion, aortic dissection is a multifactorial disease and this diagnosis must be in mind for patients presenting with acute severe chest pain, especially in the presence of risk factors, so that proper treatment initiates before becoming too late. One of these risk factors might be prior history of drug abuse especially cocaine abuse; when other risk factors are added, the cumulative likelihood effect is exponentially increased.

So far Bentall surgery is the gold standard for the treatment of TAA, although David procedure is an attractive alternative for patients with intact aortic valve (18). Invaluable role of intraoperative TEE is also noteworthy, especially when there is not adequate time for preoperative echocardiography (19). Beta-blockers and angiotensin 2 blockers are also utilized in patients with MFS in order to reduce the stress wall, Angiotensin-converting enzyme inhibitors and calcium channel blockers are also alternatives to achieve this goal. In more recent animal studies protective effects of TGF-B neutralization, doxycycline and statins were suggested, however, further evaluation is necessary to confirm clinical efficacy in human (18).

In the last decades, patient-specific models have become popular since they permit investigating cell models specific to each patient. Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) are favorable tools to investigate the pathophysiology of the underlying disease and discovering appropriate drugs to treat MFS (9). Besides such tools offer the advantage of being patient-specific, yet still are under investigation.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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