rehabilitation. During follow-up at outpatient clinic, his symptom did not change.

Comment

Paraplegia after cardiac surgery is a rare complication. There are some articles reporting spinal cord infarction after coronary artery surgery [1–4]. In those cases, highly likely mechanism of spinal cord infarction could be microembolization of atherosclerotic plaque or cholesterol emboli from the aorta. In our case, the patient did not have a history of hypertension, hyperlipidemia, diabetes, or peripheral vascular diseases. Before manipulating cardiopulmonary bypass, epiaortic echography was performed, which showed there was no particular atherosclerotic plaque at the ascending aorta. Therefore, we might suggest atherosclerotic disease did not influence paraplegia significantly in this patient. The MRI revealed that the cause of paraplegia of this patient was intramedullary hemorrhage. There seems to be a difference on the cause of paraplegia between reported cases (infarction) and our case (hemorrhage).

Intramedullary hemorrhage is commonly caused by trauma, vascular malformation, or bleeding diatheses [5]. This patient took Coumadin before surgery for atrial fibrillation and discontinued 4 days before surgery. The PT-INR on admission was 2.4. Three days before surgery, the patient complained of left-sided back pain. Electrocardiogram, chest X-ray, brain computed tomography, and blood data did not show any significant changes. Pain was controlled by conventional analgesia. Retrospectively thinking, the patient might be complicated with small intramedullary hemorrhage due to preoperative anticoagulation therapy, when he complained of back pain preoperatively. It may be presumed that during cardiac surgery with general heparinization, the size of hemorrhage increased. Consequently, the hemorrhage caused paraplegia after surgery. We might suggest that the patient should have been examined with MRI, which was the only one modality for diagnosing intramedullary hemorrhage. This report suggests that intramedullary hemorrhage may occur with usual oral anticoagulation therapy and after cardiac surgery.

References


Novel TGFBR2 and Known Missense SMAD3 Mutations: Two Case Reports of Thoracic Aortic Aneurysms

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We report the clinical presentation and genetic screening of 2 patients with thoracic aortic aneurysms. A novel TGFBR2 mutation in the 5’ untranslated region (c.-59C>T) was identified in a 31-year-old man with a Stanford type A aortic dissection. Bioinformatics tools showed that c.-59C>T variant was predicted to affect exonic splicing enhancer, as validated by quantitative real-time RT-PCR, revealing a sixfold increase of TGFBR2 mRNA in aneurysmal aortic tissue collected during surgery. A previously described missense mutation, p.E239K, in the SMAD3 gene was identified in a 60-year-old man who presented with diffuse vasculopathy. These findings suggest that the features of aneurysmal disease extending beyond the ascending aorta may help to target SMAD3 genetic screening and that alterations in the core splicing machinery can contribute to aneurysmal disease.

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Thoracic aortic aneurysm (TAA) is a major disease affecting the aorta, typically asymptomatic, leading to an acute aortic dissection with life-threatening complications including sudden catastrophic death [1]. Recent evidence highlighted a dysregulation of transforming growth factor-beta (TGF-β) signaling in ascending TAA [1]. Accordingly, mutations in the genes that encode the TGF-β receptors (TGFBR1 and TGFBR2) have been identified as a cause of familial thoracic aortic aneurysms and dissections (TAAD) [2].

Exome sequencing of the SMAD3 gene in families with multiple members with TAA and acute aortic dissections identified mutations in 2% of familial cases of TAA, in particular in families having diffuse vasculopathy extending beyond the ascending aorta [3]. We report 2 unrelated patients with familial TAA, 1 associated with a novel TGFBR2 mutation and 1 with a previously reported SMAD3 missense mutation, discussing implications for management and treatment as well as new research perspectives. This study was conducted with informed consent.

Accepted for publication Feb 11, 2014.

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consent of the subjects and was approved by the local Ethical Research Committee.

Case Reports

Patient 1
A 31-year-old man with a family history of TAAD, whose father had died suddenly at a young age from an acute aortic dissection and rupture of the ascending aorta, was admitted to the emergency department with severe, sudden onset abdominal pain. A computed tomography (CT) scan diagnosed a Stanford type A aortic dissection with hypoperfusion of left renal and superior mesenteric arteries and obstruction of the right internal carotid artery, and the echocardiogram showed a massive aortic insufficiency. He was referred to our cardiac surgery department at Fondazione Toscana G. Monasterio in Massa, Italy, for an emergent operative repair. The surgical report confirmed type A aortic dissection extending from the tricuspid aortic valve to the thoracic aorta with dilation of aortic annulus and aortic root, multiple intimal tears at the level of ascending aorta, branch vessel involvement, and hemopericardium.

The replacement of the ascending aorta, aortic arch, and aortic root was performed. A mutational screening of TGFBR1, TGFBR2, and SMAD3 genes was performed by direct gene sequencing on genomic DNA extracted from blood samples. Exons and the flanking intronic sequences were amplified by polymerase chain reaction (PCR) using specific primers as previously described [3,5]. Sequencing of the TGFBR2 gene showed the presence of a novel mutation in the 5‘untranslated region (c.-59C>T). The identified mutation was assessed to be absent in 200 ethnically referenced alleles derived from volunteers by PCR-based restriction fragment length polymorphism. This mutation was tested by the bioinformatics tool Human Splicing Finder (www.umd.be/hsf/) [4] to evaluate the effect of the variant on the splicing regulation. The bioinformatics analysis showed that c.-59C>T variant was predicted to affect exonic splicing enhancer (ESE), as seen in Figure 1. To investigate the effect of the predicted splicing alteration, real-time PCR and quantitative PCR were performed on ascending aortic tissues collected from patients with sporadic TAA who underwent aorta replacement. The genetic screening excluded the presence of the c.-59C>T mutation in the TGFBR2 gene in these patients. Gel electrophoresis of the PCR products showed the absence of aberrantly spliced transcripts in the messenger RNA studied, while TGFBR2 expression levels, in the patient harboring c.-59C>T, were increased by almost sixfold compared with aortic samples from patients not having the mutation (p = 0.0004, t test; n = 6; Fig 2).

Patient 2
The patient was a 60-year-old man with a positive family history for vascular disease; in particular, his nephew had died suddenly from intracranial aneurysms at 20 years old. Serial CT scans showed a diffuse vascular disease characterized with dilations or aneurysms involving various arteries, including the thoracic, abdominal aorta, iliac, renal, femoral, and intracranial...
Importantly, new recent insights have indicated that diverging alternative splicing in the differential splicing is a common feature of TAA formation. In our patient, we found a novel mutation in the untranslated region of TGFBR2 gene, c.-59C>T, that is predicted to disrupt protein function, p.E239K, in the MH2 domain that is predicted to disrupt protein function [3].

Comment

We report the cases of 2 unrelated patients with thoracic aortic aneurysm or dissection associated with one novel mutation in the TGFBR2 gene and one previously reported SMAD3 mutation, respectively. Tran-Fadulu et al [5] showed that patients with TGFBR2 mutations are more likely to dissect at aortic diameters less than 5.0 cm than persons with TGFBR1 mutations, suggesting that they should receive diligent lifelong cardiovascular surveillance and aggressive surgical management when the diagnosis is familial TAA [5]. In our patient, we found a novel mutation in the 5’untranslated TGFBR2 region that is predicted to affect the splicing regulatory elements, such as ESE. Indeed, the presence of mutation c.-59C>T in this ESE of TGFBR2 gene leads to an increased expression by almost sixfold compared with wild-type genotypes, highlighting the importance of the splicing process in the pathogenesis of TAA.

Importantly, new recent insights have indicated that differential splicing is a common feature of TAA formation and in particular, that the diverging splicing in the TGF-β pathway may be an important process in aneurysmal disease [6]. Our findings suggest a potential value for evaluating variants that affect splicing regulatory elements, leading to abnormal expression even if they do not influence splicing. SMAD3 encodes a protein involved in downstream cellular signaling initiated by TGF-β binding to its receptors.

Recently, exome sequencing has identified that SMAD3 mutations are responsible for 2% of familial TAAD, particularly in families with TAAD alone, along with families with inheritance of a combined phenotype of TAAD, intracranial aneurysms, and abdominal aortic aneurysms segregating in an autosomal dominant manner [3]. Interestingly, our patient carried a missense mutation previously identified by Regalado and associates [3] in a family of European descent that is predicted to disrupt protein function. Recently, Van de Laar and colleagues [7] recommended that SMAD3-associated disease should be regarded as an aggressive aneurysm syndrome, demanding early diagnosis, surveillance of the entire arterial tree, and prophylactic surgical intervention.

In conclusion, our findings confirm that the features of aneurysmal disease extending beyond the ascending aorta may help target SMAD3 genetic screening and that alterations in the core splicing machinery can contribute to aneurysmal disease.

We thank Roberto Guarino for bioinformatics analysis and Andrea Borghini for his support in qRT-PCR analysis.

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