Recurrent spontaneous coronary dissections in a patient with a de novo fibrillin-1 mutation without Marfan syndrome

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Dear Sirs,

Among the causes of myocardial infarction, spontaneous coronary artery dissection (SCAD) is rare and underdiagnosed, owing to the limited accuracy of coronary angiography. Without occlusion, SCAD can remain asymptomatic. The largest series comprised 23 cases from >11,000 coronary angiograms at Vancouver General Hospital and 87 retrospectively identified cases that occurred 1979–2011 at the Mayo clinic (1). Conditions predisposing for SCAD include vascular syndromes and fibromuscular dysplasia. Little is known, however, about underlying molecular mechanisms.

We report SCAD in a 46-year-old male patient without cardiovascular risk factors or family history, who presented with acute myocardial infarction (MI) due to an occlusive dissection of the left circumflex coronary artery and four years later with spiral dissection of the left anterior descending (LAD) coronary artery in the absence of atherosclerotic plaques (Figure 1A, B). Neither event was preceded by excessive physical stress. The patient underwent comprehensive cardiovascular diagnostics, whole exome sequencing, and analysis of smooth muscle progenitor cell (SPC) abundance and function using flow cytometry and a scratch-induced migration assay.

Echocardiography, computed tomography and magnetic resonance angiography excluded ectasia and fibromuscular dysplasia of medium-sized or large arteries including the aorta. Screening of candidate genes for arterial dissection revealed a de novo missense mutation in the Marfan gene FBN1 (c.4214T>G), which is presumed to be pathogenic, as well as paternally transmitted missense variants in myosin light-chain kinase (c.1609G>A) and in the SKI gene (c.2007C>G), both predicted to be benign. The patient neither displayed features of Shprintzen-Goldberg-syndrome, nor did he fulfill the criteria of the revised Ghent nosology for Marfan syndrome and related conditions (2), except displaying a minor mitral valve prolapse. The heterozygous FBN1 mutation at the beginning of exon 34 led to a rare exchange of apolar leucin 1405 into polar arginine. Significant aberrant splicing was excluded by RNA sequencing.

Increased transforming growth factor (TGF)-β levels and signalling have been implicated in aneurysm formation and arterial dissection in Marfan patients (3). As opposed to Marfan patients with FBN1 mutations but in line with the non-Marfanoid-phenotype of our patient, his TGF-β plasma levels were not elevated (Figure 1C). Arterial stiffness as determined by aortic pulse wave velocity was low (6.7 ± 0.3 m/s, 5th percentile of age-matched controls), differing from findings in Marfan patients. Serum fibrillin-1 levels were unaltered. Searching for alternative mechanisms, we found that circulating SPCs, which are involved in arterial remodeling (4), were more abundant in peripheral blood of our patient, as compared to age-matched healthy controls (Figure 1D). Functionally, his SPCs showed increased proliferation and migration in vitro, thereby improving scratch-wound recovery, whereas knockdown of fibrillin-1 reduced wound recovery to comparably low levels in our patient and controls, confirming its role in SPC migration and suggesting a FBN1-dependent gain-of-function in our patient (Figure 1E).

To our best knowledge, we report the first case of SCAD with a FBN1 mutation, which intriguingly is not associated with a Marfan phenotype. Software based prediction plays an important role in assessing the pathophysiological relevance of a non-synonymous single-nucleotide polymorphism (SNP). Unfortunately, different prediction algorithms use different information, which at times results in incongruent predictions. In our case, “SIFT” and “PolyPhen2” classify the SNP as tolerated, albeit with suboptimal confidence, whereas “Mutation Taster” classifies the variant as disease-causing. Amongst others, the strong decrease in hydrophobicity and the high phylogenetic conservation of the neighbouring sequence were considered, defining a need for further functional experiments. Indeed, biochemical and functional parameters corroborated that the SNP does not mediate changes seen in Marfan syndrome but rather imply distinct pathomechanisms related to SPCs. The elevated number and enhanced migratory behaviour of SPCs may give rise to structural alterations increasing the susceptibility to arterial dissection. Supportive of a role in SCAD, this FBN1 mutation was also present in a patient with thoracic aortic dissection without aneurysm or Marfan syndrome.

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syndrome (5) and a deceased case in the Regensburg MI family study (Y. von Kodolitsch, C. Hengstenberg, personal communications). As a caveat, the mutation was identified in 4 of 4000 in-house exomes including children without known vascular manifestations but none of over 60,000 exomes from the Exome Aggregation Consortium (6), indicating incomplete penetrance. Fibrillin-1 is a large protein engaging in various molecular interactions and functions. Mutations resulting in a Marfan phenotype can affect multiple or general pathways such as TGF-β mediated processes, whereas the mutation described herein clearly seems to be related to an altered SMC phenotype, but not to increased TGF-β levels. In summary, the rare allele frequency in combination with a very rare phenotype, the de novo occurrence and the related phenotype of another individual with the same mutation argue in favour of causality. Moreover, we detected alterations of SPC function using in vitro assays, acknowledging that these are not standardised and could not be performed in other carriers owing to a lack of available material. On the other hand, one adult individual with the same mutation (Regensburg MI family study) died at 65 years of age with extensive atherosclerotic and tumour disease, implying that, even if the FBN1 mutation is causal, its penetrance will not be 100%. Our findings may warrant individual genetic analysis in suspected cases of SCAD to unveil common patho-mechanisms responsible for this challenging entity.

Figure 1: Smooth muscle progenitor cells (SPCs) in a patient with SCAD differ in number and function. Angiogram (RAO 40/20) showing a spontaneous spiral dissection (arrows) of the left anterior descending (LAD) coronary artery before (A) and after percutaneous coronary intervention (B). C) Total TGF-β levels were determined in plasma in comparison with age-matched healthy controls (N=56) and Marfan patients (N=46) with FBN1 mutations by ELISA and analyzed by two-sided t-test (* P<0.01 vs controls). D) Circulating platelet-derived growth factor receptor (PDGFR)-β+ and VEGF receptor-negative CD45lowCD34+ SPCs were quantified in duplicate by flow cytometry relative to total CD45+ leukocytes in the patient versus healthy controls (N=10). E) After scratch-induced injury of confluent SPC-derived outgrowth cell monolayers, migration and proliferation were studied by analysing the area recovered by SPCs in multiple fields after 8 h. In both patient and control SPCs, knockdown of FBN1 was performed by transfection with silencing siRNA. Data are mean ± SEM.
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Conflicts of interest
None declared.

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