Familial Spontaneous Coronary Artery Dissection and the SMAD-3 Mutation

Amir Solomonica, MD, MPH[a,b], Rodrigo Bagur, MD, PHD[a,b], Tawfiq Choudhury, MBBS, MD (Res)[a,b], and Shahar Lavi, MD[a,b,*]

Spontaneous coronary artery dissection (SCAD) is a cause of about 4% of acute coronary syndrome. The pathophysiology of SCAD is not yet fully understood. Loeys-Dietz syndrome is a connective tissue disorder characterized by aortic aneurysms, arterial tortuosity, and aortic dissections. It is caused by mutations in the genes affecting the transforming growth factor β pathway. We describe a family with a SMAD3 gene mutation and Loeys-Dietz syndrome presenting with recurrent SCAD episodes. **(Am J Cardiol 2019;124:313−315)**

The true prevalence of spontaneous coronary artery dissection (SCAD) is unclear, but recent data suggests it may be the culprit in up to 4% of acute coronary syndromes.[1,2] Although first described in 1931, SCAD's pathophysiology is still not fully understood. According to small series, an identifiable genetically triggered cause for SCAD was found in only 5% to 8% of the patients.[3,4] Loeys-Dietz syndrome (LDS), first described in 2006,[5] is an autosomal dominant connective tissue disorder with variable expression characterized typically by aortic aneurysms, arterial tortuosity and dissections, hypertelorism, bifid/broad uvula or cleft palate and early onset osteoarthritis.[6] Mutations in the genes encoding transforming growth factor β receptors 1 and 2 and SMAD3 were shown to be involved. The association between LDS and SCAD has only rarely been described,[7−9] but coronary artery tortuosity, which is one of the cornerstones of LDS, was found to be prevalent in SCAD patients and was associated with recurrent SCAD episodes.[10] It had been proposed that a mutation in any of these genes and a documented arterial aneurysm or dissection should suffice to make a diagnosis of LDS and more specifically in the case of SMAD3 mutations—LDS type 3.[11,12]

Case

The proband is a 34-year-old woman which presented in 2008 with what was considered to be a non-ST elevation myocardial infarction. Her past medical history was negligible and risk factors consisted only of previous smoking. Coronary angiography demonstrated mild narrowing of the left anterior descending artery which, at the time, was not recognized as SCAD. She was asymptomatic until 2012 when she presented with another episode of non-ST elevation myocardial infarction. This time, coronary angiography revealed an acute occlusion of the right posterior descending artery (Figure 1). Percutaneous coronary intervention was attempted but was unsuccessful (Figure 1). Review of the films for the purposes of this report suggested previously unnoticed concomitant SCAD in 2 diagonal branches but with good flow (Figure 1). The patient was discharged home and had done well. In 2015, she presented again with chest pain, ischemic electrocardiogram changes and elevation in troponin. Coronary angiography revealed narrowing of the right posterolateral artery consistent with SCAD type IIA (Figure 1). Complete healing of the previously affected posterior descending artery and diagonals was noticed (Figure 1). Medical management was advised but she presented again 2 weeks later with myocardial infarction and occlusion of the posterolateral artery. She presented again in 2019 with chest pain, and this time was diagnosed with a type A aortic dissection and had subsequently undergone a valve sparing aortic root reconstruction and hemiarch reconstruction.

In 2018, the patient's 41-year-old brother presented with chest pain and mild elevation in troponin. Coronary angiography revealed diffuse narrowing of the distal part of the left anterior descending artery consistent with SCAD type IIB (Figure 1). He was managed conservatively and remained asymptomatic.

During this period, 2 of the proband's uncles had died at the age of 40 due to aortic dissections. Consequently, genetic workup was undertaken and a mutation (c.860 G>A p.Arg287Gln) in the SMAD3 gene were found in several family members including the proband and her brother as shown in the pedigree chart, and accordingly a diagnosis of LDS type III had been made (Figure 2). This mutation located in exon 6 and encoding for a part of a well preserved MH2 domain of the protein had been described before and is believed to be pathogenic.[9,12] Of note, physical examination had not revealed other phenotypic traits relating to LDS in the proband, but the brother did have arthritis in right hip which necessitated surgery.

Discussion

SCAD is more prevalent than previously believed and the diagnosis rate is constantly increasing yet its pathophysiology is still not entirely understood. Currently, routine genetic screening for patients presenting with SCAD is not recommended due to the relatively low yield found in

[a]Western University, London Health Sciences Centre London, Ontario, Canada; and [b]Department of Medicine, London Health Sciences Centre London, Ontario, Canada. Manuscript received March 14, 2019; revised manuscript received and accepted April 9, 2019.

*Corresponding author: Tel: +15196633611.

E-mail address: Shahar.Lavi@lhsc.on.ca (S. Lavi).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.04.035

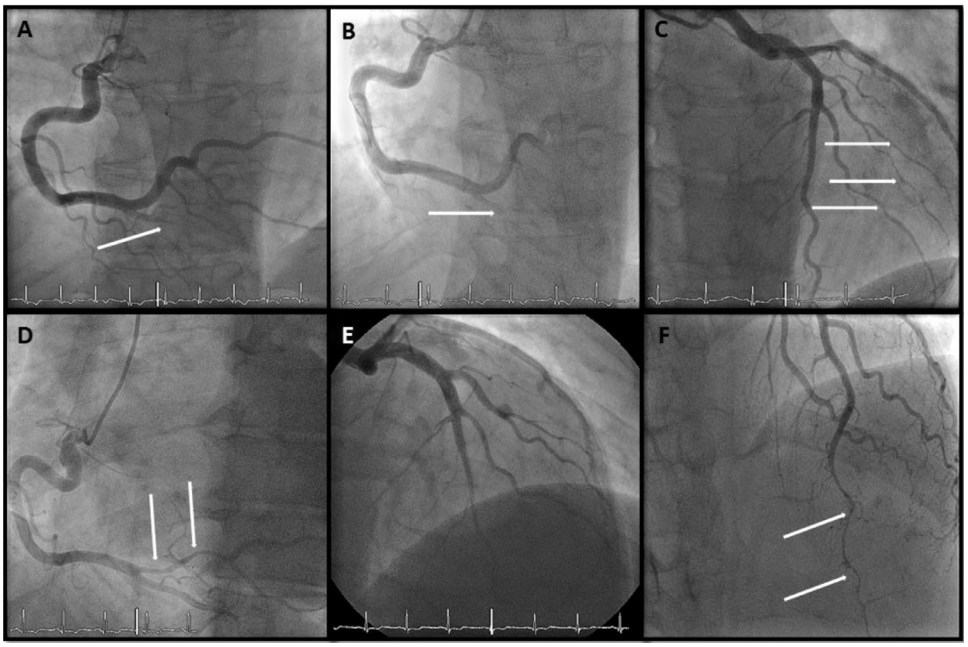

Figure 1. Patient's initial presentation with acute occlusion of Rt. PDA (***A***) PCI attempted but unsuccessful (***B***). Concomitant SCAD type IIA in 2 diagonal branches (***C***). Patient presenting again with SCAD type IIA in Rt. posterolateral branch (PLB). The Rt. PDA healed (***D***) as did the diagonals (***E***). The patient's brother presenting with SCAD type IIB in LAD (***F***). PCI = Percutaneous coronary intervention; PDA = posterior descending artery.

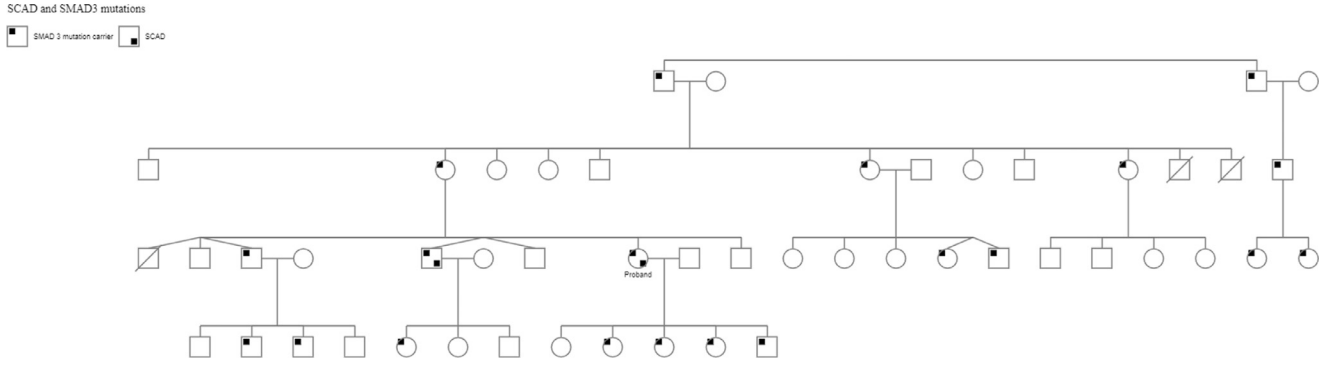

Figure 2. Family pedigree.

previously published small series.[1] In the recently published 30-day follow-up results of the Canadian SCAD cohort, connective tissue diseases and family history of SCAD were identified in a minority of the cases;[13] 6.1% of the cohort patients had recurrent events within the first 30 days. Previous data suggests that the rate of recurrent SCAD is 15% to 22% at 2 to 3 years of follow-up and up to 30% at 4 to 10 years, but the reported rates vary considerably between the different relatively small series.[14,15] Our data may suggest that patients with connective tissue disorders may be more likely to experience recurrences, but this obviously requires further investigation.

To date only small series dealt with the potential association between genetic mutations and SCAD. Data regarding the prognosis and management of patients with genetic mutations predisposing to SCAD are still lacking. Although LDS type 3 has been shown to represent 2% of familial thoracic aorta aneurysms and dissections its role in familial SCAD, a rare entity by its own, is unknown.[16] Due to the higher risk for arterial aneurysms and dissections a full body computed tomography/magnetic resonance imaging is advised for LDS patients as well as an echocardiogram follow up.[11,12]

We suggest genetic assessment to be done when there are repeated episodes of SCAD or when SCAD affects multiple family members.

1. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, Ganesh SK, Gulati R, Lindsay ME, Mieres JH, Naderi S, Shah S, Thaler DE, Tweet MS, Wood MJ. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. *Circulation* 2018;137:e523–e557.
2. Choudhury T, Solomonica A, Bagur R, Lavi S. Intravascular imaging for cardiac arrest with "normal" coronary arteriography. *Cardiovasc Revasc Med* 2018;19:53–55.
3. Henkin S, Negrotto SM, Tweet MS, Kirmani S, Deyle DR, Gulati R, Olson TM, Hayes SN. Spontaneous coronary artery dissection and its association with heritable connective tissue disorders. *Heart (British Cardiac Society)* 2016;102:876–881.

4. Kaadan MI, MacDonald C, Ponzini F, Duran J, Newell K, Pitler L, Lin A, Weinberg I, Wood MJ, Lindsay ME. Prospective cardiovascular genetics evaluation in spontaneous coronary artery dissection. *Circ Genom Precis Med* 2018;11:e001933.
5. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, Roberts AE, Faravelli F, Greco MA, Pyeritz RE, Milewicz DM, Coucke PJ, Cameron DE, Braverman AC, Byers PH, De Paepe AM, Dietz HC. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Eng J Med* 2006;355:788–798.
6. van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, Hoedemaekers YM, Willemsen R, Severijnen LA, Venselaar H, Vriend G, Pattynama PM, Collee M, Majoor-Krakauer D, Poldermans D, Frohn-Mulder IM, Micha D, Timmermans J, Hilhorst-Hofstee Y, Bierma-Zeinstra SM, Willems PJ, Kros JM, Oei EH, Oostra BA, Wessels MW, Bertoli-Avella AM. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. *Nat genet* 2011;43:121–126.
7. Vanzetto G, Berger-Coz E, Barone-Rochette G, Chavanon O, Bouvaist H, Hacini R, Blin D, Machecourt J. Prevalence, therapeutic management and medium-term prognosis of spontaneous coronary artery dissection: results from a database of 11,605 patients. *Eur J Cardiothorac Surg* 2009;35:250–254.
8. Fattori R, Sangiorgio P, Mariucci E, Ritelli M, Wischmeijer A, Greco C, Colombi M. Spontaneous coronary artery dissection in a young woman with Loeys-Dietz syndrome. *Am J Med Genet A* 2012;158a:1216–1218.
9. Aubart M, Gobert D, Aubart-Cohen F, Detaint D, Hanna N, d'Indya H, Lequintrec JS, Renard P, Vigneron AM, Dieude P, Laissy JP, Koch P, Muti C, Roume J, Cusin V, Grandchamp B, Gouya L, LeGuern E, Papo T, Boileau C, Jondeau G. Early-onset osteoarthritis, Charcot-Marie-Tooth like neuropathy, autoimmune features, multiple arterial aneurysms and dissections: an unrecognized and life threatening condition. *PloS One* 2014;9:e96387.
10. Eleid MF, Guddeti RR, Tweet MS, Lerman A, Singh M, Best PJ, Vrtiska TJ, Prasad M, Rihal CS, Hayes SN, Gulati R. Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circ Cardiovasc Interv* 2014;7:656–662.
11. MacCarrick G, Black JH 3rd, Bowdin S, El-Hamamsy I, Frischmeyer-Guerrerio PA, Guerrerio AL, Sponseller PD, Loeys B, Dietz HC 3rd. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med* 2014;16:576–587.
12. Schepers D, Tortora G, Morisaki H, MacCarrick G, Lindsay M, Liang D, Mehta SG, Hague J, Verhagen J, van de Laar I, Wessels M, Detisch Y, van Haelst M, Baas A, Lichtenbelt K, Braun K, van der Linde D, Roos-Hesselink J, McGillivray G, Meester J, Maystadt I, Coucke P, El-Khoury E, Parkash S, Diness B, Risom L, Scurr I, Hilhorst-Hofstee Y, Morisaki T, Richer J, Desir J, Kempers M, Rideout AL, Horne G, Bennett C, Rahikkala E, Vandeweyer G, Alaerts M, Verstraeten A, Dietz H, Van Laer L, Loeys B. A mutation update on the LDS-associated genes TGFB2/3 and SMAD2/3. *Hum Mutat* 2018;39:621–634.
13. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, Brass N, Lavoie A, Bishop H, Lavi S, Pearce C, Renner S, Madan M, Welsh RC, Lutchmedial S, Vijayaraghavan R, Aymong E, Har B, Ibrahim R, Gornik HL, Ganesh S, Buller C, Matteau A, Martucci G, Ko D, Mancini GBJ. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. *Eur Heart J* 2019;40:1188–1197.
14. Nakashima T, Noguchi T, Haruta S, Yamamoto Y, Oshima S, Nakao K, Taniguchi Y, Yamaguchi J, Tsuchihashi K, Seki A, Kawasaki T, Uchida T, Omura N, Kikuchi M, Kimura K, Ogawa H, Miyazaki S, Yasuda S. Prognostic impact of spontaneous coronary artery dissection in young female patients with acute myocardial infarction: a report from the Angina Pectoris-Myocardial Infarction Multicenter Investigators in Japan. *Int J Cardiol* 2016;207:341–348.
15. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, Robinson S, Vuurmans T, Gao M, Humphries K, Mancini GB. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. *Circ Cardiovasc Interv* 2014;7:645–655.
16. van der Linde D, van de Laar IM, Bertoli-Avella AM, Oldenburg RA, Bekkers JA, Mattace-Raso FU, van den Meiracker AH, Moelker A, van Kooten F, Frohn-Mulder IM, Timmermans J, Moltzer E, Cobben JM, van Laer L, Loeys B, De Backer J, Coucke PJ, De Paepe A, Hilhorst-Hofstee Y, Wessels MW, Roos-Hesselink JW. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol* 2012;60:397–403.