

Coil embolization of bilateral internal mammary artery aneurysms in the setting of a heterozygous missense variant of unknown significance in COL5A1 and fibromuscular dysplasia

Julia Fayanne Chen, MD,^a Dimitra Papanikolaou, MD,^b Arash Fereydooni, MS,^a Hamid Mojibian, MD,^c Alan Dardik, MD, PhD,^a and Naiem Nassiri, MD,^a *New Haven, Conn*

ABSTRACT

Internal mammary artery aneurysms are rare but serious clinical entities. Rupture results in hemothorax and can be life threatening. Most reported cases are pseudoaneurysms secondary to iatrogenic or traumatic causes. Noniatrogenic, nontraumatic, true internal mammary artery aneurysms have most commonly been associated with vasculitides or connective tissue disorders; rare cases have been deemed idiopathic. We describe a rare case of bilateral internal mammary artery aneurysms—successfully treated with coil embolization—in the setting of heterozygosity for a missense variant of unknown significance in the COL5A1 gene and multifocal fibrodysplastic changes on angiography. (*J Vasc Surg Cases and Innovative Techniques* 2019;5:410-4.)

Keywords: Internal mammary artery aneurysm; Coil embolization; Fibromuscular dysplasia

True internal mammary artery aneurysms are rare. The majority of published reports describe iatrogenic or traumatic pseudoaneurysms.¹ Only 14 cases to date have described noniatrogenic internal mammary artery aneurysms caused by vasculitides, connective tissue disorders, and rarely idiopathic etiology.¹⁻¹⁴ Bilateral internal mammary artery aneurysms are even less common, with only two published reports, both describing patients with Marfan syndrome.^{6,9}

Internal mammary artery aneurysms have traditionally been managed surgically, and endovascular repair has only recently been described. Herein, we present a rare case of bilateral internal mammary artery aneurysms treated simultaneously with transbrachial coil embolization in the setting of heterozygosity for a missense variant of unknown significance in COL5A1, and multifocal fibromuscular dysplasia (FMD). The patient described here has consented to publication of all case details and associated images.

CASE REPORT

Presentation. A 62-year-old man, former smoker (10 pack-year history), with no known history of vascular disease, trauma, or previous surgical procedures, presented to the emergency department with acute exacerbation of ongoing chest pain of 6 months' duration, worse with exertion. Acute coronary syndrome, pulmonary embolism, chronic obstructive pulmonary disease, and infectious etiologies were ruled out. Computed tomography angiography (CTA) revealed aneurysms in multiple arterial beds (Table and Fig 1, A, B), including bilateral internal mammary arteries (right 1.6 cm, left 1.1 cm; Fig 2, A)—normal internal mammary artery diameter being approximately 2.5 mm^{15,16}—multiple intercostal arteries, right subclavian artery (2.1 cm), celiac artery (1.4 cm), right renal artery, and bilateral iliac arteries (right 1.8 cm, left 2.4 cm). A “string-of-beads” appearance was noted in the intercostal arteries (Fig 2, B), suggestive of fibromuscular dysplasia, multifocal type. Given the patient's presenting symptoms as well as the size and saccular nature of the internal mammary artery aneurysms, treatment was warranted. The decision was made to proceed with a minimally invasive endovascular approach.

Surgical technique. Via retrograde transbrachial access, selective catheterization of the proximal subclavian arteries was performed bilaterally. Angiography was performed in multiple views confirming CTA findings (Fig 3, A). Under roadmap guidance, a coaxial system—comprised of a 5F short sheath, a 5F C2 catheter (Cook Medical, Bloomington, Ind), and a 2.7F, 45° angled tip, high-flow Lantern microcatheter (Penumbra, Alameda, Calif)—was used to selectively catheterize the distal outflow of the aneurysms bilaterally. Mechanically detachable Ruby POD and packing coils (Penumbra) were used to first form a distal plug, and then pack the outflow, sac, and inflow of aneurysms bilaterally with good deposition and no evidence of nontarget embolization (Fig 3, B). No coil extrusion into the feeding subclavian arteries was noted. Aneurysm sac devascularization was confirmed on completion angiography at follow-up visits (Fig 3, C-F).

From the Division of Vascular and Endovascular Surgery^a; the Division of Cardiac Surgery and The Yale Aortic Institute,^b Department of Surgery; and the Department of Radiology and Biomedical Imaging,^c Yale University School of Medicine.

Author conflict of interest: N.N. is a member of the speakers' bureau and consultant for Penumbra, Inc.

Correspondence: Naiem Nassiri, MD, Associate Professor of Surgery (Vascular), Yale School of Medicine, Yale New Haven Hospital, Chief, Vascular & Endovascular Surgery, VA Connecticut Healthcare System, Boardman Bldg, 330 Cedar St, New Haven, CT 06510 (e-mail: naiem.nassiri@yale.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2468-4287

© 2019 The Author(s). Published by Elsevier Inc. on behalf of Society for Vascular Surgery. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jvscit.2019.07.002>

Table. Summary of aneurysms found on computed tomography angiography (CTA)

Location	Laterality	Maximum diameter
Internal mammary artery	Bilateral	Right 1.6 cm, left 1.1 cm
Subclavian artery	Right	2.1 cm
Celiac artery	N/A	1.4 cm
Renal artery	Right	Ectatic 1 cm
Iliac artery	Bilateral	Right 1.8 cm, left 2.4 cm
Multiple intercostal arteries (T6-T12)	Bilateral	8 mm

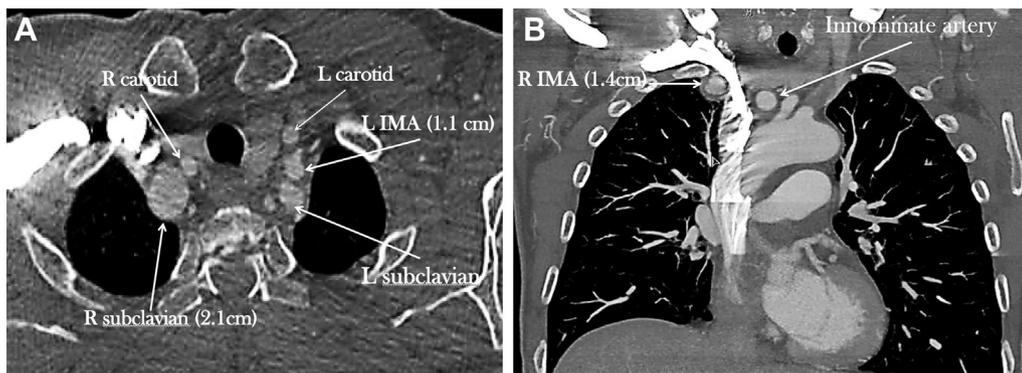


Fig 1. Preoperative computed tomography angiography (CTA) of the chest. **A**, Aneurysmal left internal mammary artery (LIMA) and right subclavian artery on CTA. **B**, Coronal view of aneurysmal right internal mammary artery (RIMA).

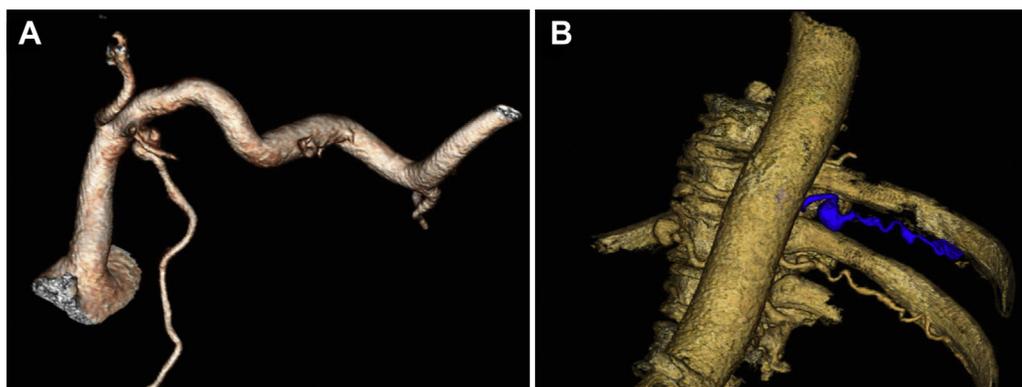


Fig 2. Three-dimensional reconstructions. **A**, Aneurysmal left internal mammary artery. **B**, Intercostal artery aneurysm with string-of-beads appearance.

Postoperative course. The patient did well after the procedure, with no complications and reported resolution of chest pain on the first postoperative day. Genetic testing was performed, and the results were notable for a heterozygous missense variant of unknown significance in the COL5A1 gene, which encodes type V collagen.¹⁷ Follow-up CTA at 6 months and 1 year demonstrated no recurrence of flow within or expansion of the embolized aneurysm sacs. The remainder of the aneurysms are currently managed by observation with serial imaging.

DISCUSSION

Limited literature exists regarding the etiology and management of true internal mammary artery aneurysms. Noniatrogenic cases have been attributed to connective tissue disorders including Marfan, Ehlers-Danlos, Loeys-Dietz, and SMAD3 mutation syndromes; in addition to other systemic vascular disorders including polyarteritis nodosa, FMD, and atherosclerosis. Only one other case of internal mammary artery aneurysm in a patient with FMD has previously been reported; and no

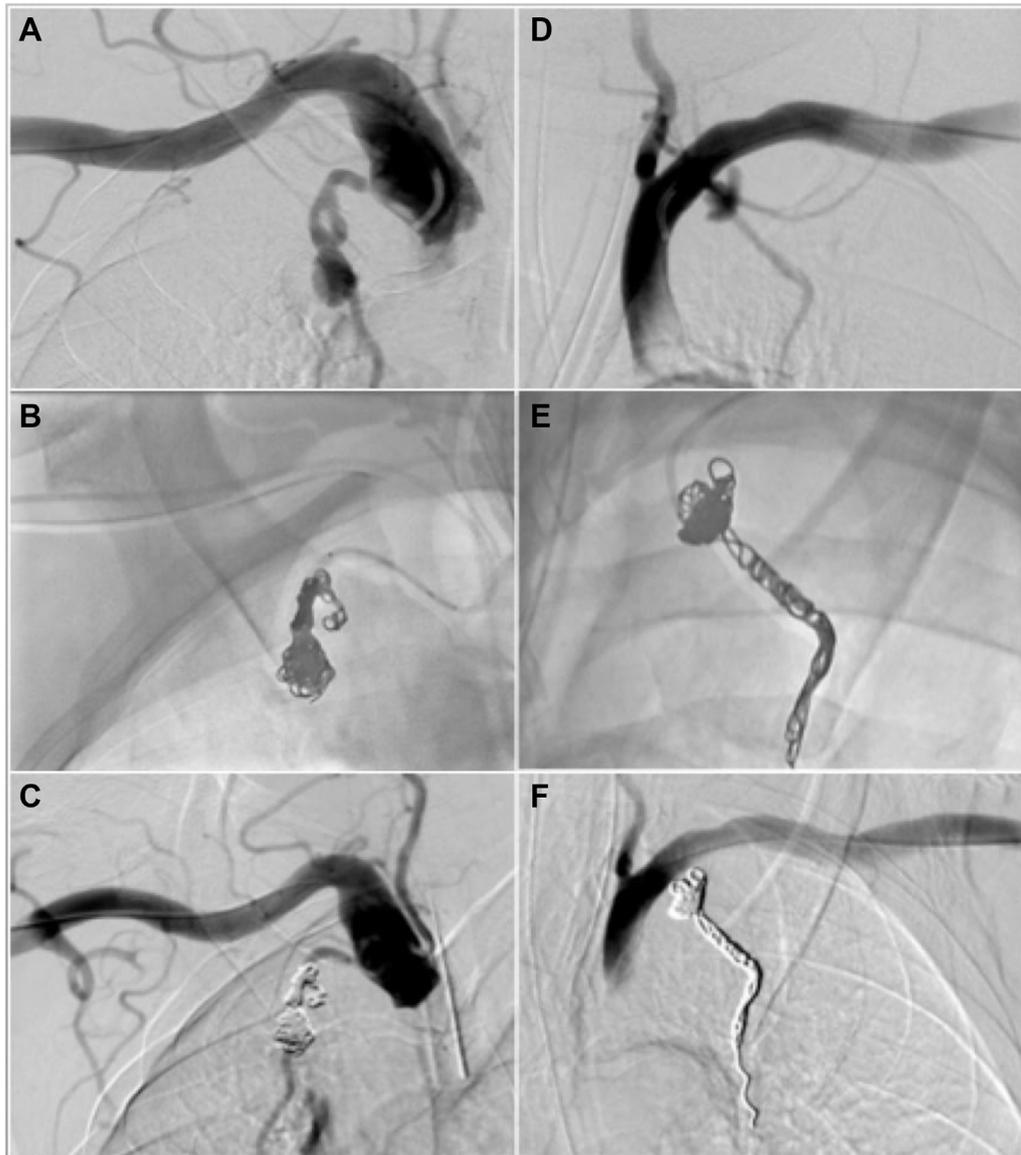


Fig 3. Intraoperative imaging. **A**, Selective catheterization of right subclavian artery and right internal mammary artery (**B**) followed by microcoil embolization and (**C**) completion angiography. **D**, Selective catheterization of left subclavian artery and left internal mammary artery (**E**) followed by microcoil embolization and (**F**) completion angiography.

treatment was undertaken in that report.¹¹ Presented here is an extremely rare case of bilateral internal mammary artery aneurysms in a 62-year-old man with angiographic evidence of multifocal FMD, as well as heterozygosity for a missense variant in COL5A1—a gene implicated in Ehlers-Danlos syndrome with type V collagenopathy. This variant (p.C1746S), classified as a variant of unknown significance, has not been reported before in the general population and is located at a highly conserved residue in evolution. It results in the substitution of a cysteine residue by serine, which usually leads to failure of collagen chain incorporation into

trimers. This variant is also predicted to be deleterious for protein function by online prediction tools. Although there is not enough evidence yet to prove this mutation is disease-causing, its rarity, location in a highly conserved region in evolution, and the fact that it is damaging to protein function point to probable pathogenicity. The patient's phenotype of multifocal aneurysmal disease could be explained by a disorder in the Ehlers-Danlos syndrome spectrum.

Although COL5A1 is not implicated in vascular Ehlers-Danlos syndrome,¹⁸ vascular phenotypes, including arterial aneurysms and dissections, have

indeed been reported in classical Ehlers-Danlos syndrome.¹⁹ This is the most likely etiology of the aneurysms, but the fibrodysplastic changes noted on CTA cannot be excluded from the differential diagnosis. A combined, multifactorial process is another rare but plausible explanation. Although no direct link has been definitively identified between FMD and collagenopathies of various sorts, such connections have been suggested.²⁰⁻²³ Genetic testing for vascular connective tissue disorders has had a low yield in FMD²⁴ and additional molecular research to elucidate the unique genetic and environmental factors associated with the pathogenesis of FMD is necessary.

Traditionally, sternotomy has been the therapeutic approach of choice for internal mammary artery aneurysms.^{1,12-14} More recently, less invasive embolotherapeutic techniques have been described.²⁻¹⁰ Although our otherwise healthy patient may have been a candidate for potential open surgery, a minimally invasive approach was selected to minimize perioperative morbidity, particularly with the bilateral nature of his disease. A minimally invasive endovascular approach based on packing coils was safe and effective in eliminating flow through the aneurysm sacs in a durable manner. The completely detachable mechanism of release—as opposed to partially detachable and/or pushable coils—allows for maximal precision of deployment into ostial lesions at high risk for catastrophic nontarget embolization.

The treatment of bilateral internal mammary artery aneurysms has been reported twice, both in patients with Marfan syndrome and multiple previous thoracotomies for aortic repair.^{6,9} One patient was treated with placement of balloon-expandable stents across the internal mammary artery aneurysms, and the other with coil embolization. Both patients were treated in a staged fashion. To our knowledge, our report is the first to describe simultaneous embolization of bilateral internal mammary artery aneurysms using mechanically detachable coils.

Although less relevant in our patient with minimal risk factors and a negative cardiac evaluation, obliteration of the left internal mammary artery as a potential inflow source for coronary artery bypass grafting in the future is an important consideration with the currently described technique. In patients who have a cardiac history and who may require a coronary artery bypass graft in the future, preservation of the left internal mammary artery should be taken into consideration.

CONCLUSIONS

There are no established guidelines for the treatment of internal mammary artery aneurysms owing to their rarity. Increasingly, recent reports describe an endovascular approach as opposed to traditional open surgery. This report further suggests that simultaneous embolization

of bilateral internal mammary artery aneurysms using mechanically detachable packing coils is safe, durable, and effective in appropriately selected patients at the 1-year follow-up. Heterozygous variants of unknown significance can have clinical manifestations of the underlying collagenopathy that warrant surgical intervention. Further molecular investigation into possible links between FMD and various collagenopathies is warranted.

REFERENCES

1. Okura Y, Kawasaki T, Hiura T, Seki H, Saito H. Aneurysm of the internal mammary artery with cystic medial degeneration. *Intern Med* 2012;51:2355-9.
2. Kim SJ, Kim CW, Fau-Kim S, Kim S, Fau-Lee TH, Lee TH, et al. Endovascular treatment of a ruptured internal thoracic artery pseudoaneurysm presenting as a massive hemothorax in a patient with type I neurofibromatosis. *Cardiovasc Intervent Radiol* 2005;28:818-21.
3. Rose JF, Lucas LC, Bui TD, Mills JL. Endovascular treatment of ruptured axillary and large internal mammary artery aneurysms in a patient with Marfan syndrome. *J Vasc Surg* 2011;53:478-82.
4. Ohman JW, Charlton-Ouw KM, Azizzadeh A. Endovascular repair of an internal mammary artery aneurysm in a patient with Loays-Dietz syndrome. *J Vasc Surg* 2012;55:837-40.
5. Burke C, Shalhub S, Starnes BW. Endovascular repair of an internal mammary artery aneurysm in a patient with SMAD-3 mutation. *J Vasc Surg* 2015;62:486-8.
6. Alhawasli H, Darki A, Lewis BE. Endovascular repair of bilateral internal mammary artery aneurysms in a patient with Marfan syndrome—a case report. *Int J Angiol* 2016;25:e39-42.
7. Kwon OY, Kim GJ, Oh TH, Lee YO, Lee SC, Cho JY. Staged management of a ruptured internal mammary artery aneurysm. *Korean J Thorac Cardiovasc Surg* 2016;49:130-3.
8. Nevidomskye D, Shalhub S, Aldea GS, Byers PH, Schwarze U, Murray ML, et al. Endovascular repair of internal mammary artery aneurysms in 2 sisters with smad3 mutation. *Ann Vasc Surg* 2017;41:283.e5-9.
9. Fujiyoshi T, Nishibe T, Koizumi N, Ogino H. Coil embolization of bilateral internal mammary artery aneurysms is durable in a patient with Marfan syndrome. *J Vasc Surg Cases Innov Tech* 2018;4:216-9.
10. Almeray T, Paz-Fumagalli R, Farres H, Oldenburg WA, Hakaim AG. Idiopathic internal mammary artery aneurysm in the setting of aberrant right subclavian artery. *J Vasc Surg Cases Innov Tech* 2017;3:251-3.
11. Fustero Aznar JM, Guillén Subirán ME, Fernández-Aguilar Pastor AC, Calvo Beguería E, Hermoso Cuenca V. Aneurisma de arteria mamaria interna en paciente con displasia fibromuscular. *Angiología* 2017;69:261-2.
12. Phan TG, Sakulsaengrapha A, Wilson M, Wing R. Ruptured internal mammary artery aneurysm presenting as massive spontaneous haemothorax in a patient with Ehlers-Danlos syndrome. *Aust N Z J Med* 1998;28:210-1.
13. Connerly CP, Cramer SF, Cheeran D. Multiple aneurysms of the internal thoracic artery. *Ann Thorac Surg* 1995;59:1561-3.
14. Wildhirt S, Eckel L, Beyersdorf F, Satter P. Atherosclerotic aneurysm of the right internal mammary artery presenting as a mediastinal mass. *J Thorac Cardiovasc Surg* 1994;107:1535-6.
15. Walpoth BH, Schmid M, Schwab A, Bosshard A, Eckstein F, Carrel T, et al. Vascular adaptation of the internal thoracic artery graft early and late after bypass surgery. *J Thorac Cardiovasc Surg* 2008;136:876-83.

16. Karaman B, Battal B, Bozkurt Y, Bozlar U, Demirkol S, Sahin MA, et al. The anatomic evaluation of the internal mammary artery using multidetector CT angiography. *Diagn Interv Radiol* 2012;18:215-20.
17. De Paepe A, Nuytinck L, Hausser I, Anton-Lamprecht I, Naeyaert JM. Mutations in the COL5A1 gene are causal in the Ehlers-Danlos syndromes I and II. *Am J Human Genet* 1997;60:547-54.
18. Malfait F, de Paepe A. Molecular genetics in classic Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet* 2005;139C:17-23.
19. D'Hondt S, Van Damme T, Malfait F. Vascular phenotypes in nonvascular subtypes of the Ehlers-Danlos syndrome: a systematic review. *Genet Med* 2018;20:562-73.
20. Wang X, Li W, Wei K, Xiao R, Wang J, Ma H, et al. Missense mutations in COL4A5 or COL4A6 genes may cause cerebrovascular fibromuscular dysplasia: case report and literature review. *Medicine (Baltimore)* 2018;97:e11538.
21. Escamilla F, Espigares A, Hervas R, Fernandez MD, Vela R, Garcia T. [Fibromuscular dysplasia with moyamoya phenomenon in a patient with Alport's syndrome. A type IV collagen disorder]. *Rev Neurol* 2000;30:736-40.
22. Sanchez Torres C, Contreras R. [Fibromuscular dysplasia: a genetic entity related to Ehlers-Danlos syndrome]. *Arch Inst Cardiol Mex* 1974;44:571-81.
23. Schievink WI, Limburg M. Angiographic abnormalities mimicking fibromuscular dysplasia in a patient with Ehlers-Danlos syndrome, type IV. *Neurosurgery* 1989;25:482-3.
24. Poloskey SL, Kim ESH, Sanghani R, Al-Quthami AH, Arscott P, Moran R, et al. Low yield of genetic testing for known vascular connective tissue disorders in patients with fibromuscular dysplasia. *Vasc Med* 2012;17:371-8.

Submitted May 19, 2019; accepted Jul 11, 2019.