Posterior tibial artery aneurysm in a child with SMAD3 mutation

Elias Kfoury, MD,a Aaron Y. Chen, BS,a and Peter H. Lin, MD,a,b Houston, Tex; and Los Angeles, Calif

ABSTRACT
Peripheral arterial aneurysms in children are uncommon. We report a 6-year-old boy who developed a right posterior tibial artery aneurysm with symptoms including pain and pulsatile tenderness. His genetic testing revealed a SMAD3 mutation, a condition associated with familial aortic aneurysm, early-onset of osteoarthritis, and peripheral aneurysms. The posterior tibial artery aneurysm was treated with surgical resection and primary anastomosis. The patient remained free of symptoms or aneurysm recurrence in his tibial artery 2 years later. This represents the first reported case of pediatric tibial artery aneurysm linked to a SMAD3 mutation. (J Vasc Surg Cases and Innovative Techniques 2017;3:109-11.)

Arterial aneurysms in children are rare, which can be attributed to congenital cardiovascular disease, connective tissue disorders, or arteritis. A genetic abnormality, such as a SMAD3 mutation, has been linked to thoracic aortic pathologies, including aneurysm and dissection. In this report, we describe a child with a SMAD3 mutation who developed a posterior tibial artery aneurysm. Informed consent was obtained for the publication of this report.

CASE REPORT
A 6-year-old boy presented with a 2-year history of right ankle pain. He noted a progressive painful pulsatile mass located posterior to the medial malleolar region. Physical examination revealed a 2-cm × 2-cm tender posterior tibial artery aneurysm (Fig 1). There were no other physical findings, such as arthritis or joint pain, and no history of trauma to his lower extremities. His family history revealed an uncle with a thoracic aortic aneurysm who died suddenly, presumably of aneurysm rupture, at age 58 years. His paternal grandfather died suddenly in his late 50s after an acute onset of chest pain, although no definitive cause of death was known.

Comprehensive genetic testing was performed for transforming growth factor-β (TGF-β) receptor 1 (TGFBR1) and receptor 2 (TGFBR2) mutations (mutation causing Loeys-Dietz syndrome), collagen type III alpha 1 (COL3A1) mutation (mutation causing Ehlers-Danlos syndrome type IV), and SMAD3 mutations. These genetic evaluations revealed a disease-causing mutation in SMAD3.

A diagnostic angiogram showed a saccular aneurysm involving the posterior tibial artery with distal embolic occlusion of the posterior plantar artery (Fig 2). Surgical repair was performed, which entailed proximal and distal arterial control, followed by aneurysm resection and primary anastomosis of the posterior tibial artery using interrupted 7-0 polypropylene sutures (Fig 3).

The patient was discharged to home 4 days later. In subsequent follow-up visits at 2 years, the patient remained pain free without aneurysm recurrence. He continues to undergo annual surveillance duplex ultrasound imaging of bilateral extremities.
Arterial aneurysm in children is uncommon, and only <200 cases have been reported in the literature. Among them, pediatric arterial aneurysm involving the lower extremity is even rarer, with <20 patients in published reports. In a clinical review of pediatric arterial aneurysm from the University of Michigan, these researchers characterized nine pathologic factors contributing to pediatric arterial aneurysms. These etiologic factors include arterial infection, giant-cell arteritis, autoimmune connective tissue disorder, Kawasaki disease, medial degeneration disease, noninflammatory medial degeneration disease, vascular dysplasia, congenital-idiopathic condition, and extravascular process. In our patient, the etiologic factor contributing to his tibial artery aneurysm is SMAD3 mutation, which represents the first reported case linking such a genetic mutation to a lower extremity arterial aneurysm in children. Our case also underscores the important role of genetic testing when treating a child who presents with an arterial aneurysm.

Previous reports have linked SMAD3 mutation to arterial aneurysm formation. A recent study reports treatment strategies of SMAD3 mutation-associated visceral and iliac artery aneurysms by means of endovascular interventions. Burke et al reported a patient with SMAD3 mutation who developed an internal mammary artery aneurysm and underwent successful endovascular coil exclusion.

Most of the current understanding of SMAD3 mutation principally implicates an etiologic role in inherited thoracic aortic disease on chromosome 15. As a recently discovered genetic variable, SMAD3 mutation joins other identified genetic etiologic factors, including fibrillin-1 (FBN1), TCFBR1, and TCFBR2, which can result in inherited thoracic aortic abnormalities such as Loeys-Dietz syndrome and Marfan syndrome. The SMAD3 gene encodes SMAD3 protein, which plays a role in cellular signaling pathway following the binding TGF-β to the TGB-b receptors. Genetic mutations of SMAD3, which can be inherited in an autosomal-dominant fashion, can result in a syndrome characterized by aortic aneurysms and early-onset degenerative osteoarthritis.

**DISCUSSION**

Arterial aneurysm in children is uncommon, and only <200 cases have been reported in the literature. Among them, pediatric arterial aneurysm involving the lower extremity is even rarer, with <20 patients in
This condition, also known as the aneurysms-osteoarthritis syndrome, can result in aneurysms and dissections in the arterial circulation, craniofacial abnormalities, osteoarthritis, and cutaneous and skeletal anomalies.8

In an analysis of 34 patients with SMAD3 mutation, van de Laar et al9 found that cardiovascular abnormalities were present in 80%. Although aortic aneurysm and aortic dissection were the two most common vascular pathologies, approximately one-third of these patients exhibited some form of arterial aneurysms, including vertebral, pulmonary, splenic, iliac, and mesenteric artery aneurysms. Significant arterial tortuosity was detected in nearly half of these patients, which involved vertebral, internal carotid, and cerebral arterial circulation.9 Another genetic study analyzed 42 patients with SMAD3 mutation from five families with familial thoracic aortic pathologies.10 The authors reported common vascular abnormalities, including thoracic aortic aneurysm or dissection, abdominal aortic aneurysm, and iliac artery aneurysms. The patient described in this report is notable because no previous published studies have linked SMA3 mutation to a posterior tibial artery aneurysm.

CONCLUSIONS

Although other researchers have described the feasibility of endovascular treatment using coil embolization in excluding arterial aneurysm in patients with SMD3 mutation,6,7 we believe such a treatment would not result in a long-term durable success in our patient. Owing to the small vessel caliber of the posterior tibial artery in our young patient, we elected surgical repair with aneurysm resection and primary repair using interrupted polypropylene sutures. The principle of interrupted anastomosis in pediatric vascular reconstruction has been highlighted by our previous reports because this technique allows circumferential vessel growth without suture line stricture when the child continues to grow.4,11 The treatment outcome of our patient was remarkable after the surgical repair as he continued to undergo yearly ultrasound surveillance, without evidence of aneurysm recurrence.

REFERENCES

1. van der Linde D, van de Laar IM, Bertoli-Avella AM, Oldenburg RA, Bekkers JA, Mattace-Raso FU, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. J Am Coll Cardiol 2012;60:397-403.
2. Yetman RJ, Black CT. Traumatic false aneurysms of peripheral arteries in children. South Med J 1992;85:665-6.
3. Sarkar R, Coran AG, Cilley RE, Lindenuer SM, Stanley JC. Arterial aneurysms in children: clinicopathologic classification. J Vasc Surg 1991;13:47-56; discussion: 57.
4. Lin PH, Dodson TF, Bush RL, Weiss VJ, Conklin BS, Chen C, et al. Surgical intervention for complications caused by femoral artery catheterization in pediatric patients. J Vasc Surg 2001;34:1071-8.
5. Bagwell CE, Caffee HH, Talbert JL. Peripheral aneurysms in children—a link to trauma. Pediatrics 1988;82:786-8.
6. van der Linde D, Verhagen HJ, Moelker A, van de Laar IM, Van Herzeel I, De Backer J, et al. Aneurysm-osteoarthritis syndrome with visceral and iliac artery aneurysms. J Vasc Surg 2013;57:96-102.
7. 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.
8. van de Laar IM, van der Linde D, Oei EH, Bos PK, Bessem JP, Bierma-Zeinstra SM, et al. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. J Med Genet 2012;49:47-57.
9. van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 2011;43:121-6.
10. Regalado ES, Guo DC, Villamizar C, Avidan N, Gilchrist D, McCallivray B, et al. Exome sequencing identifies SMAD3 mutations as a cause of familial thoracic aortic aneurysm and dissection with intracranial and other arterial aneurysms. Circ Res 2011;109:680-6.
11. Lin PH, Barr V, Bush RL, Velez DA, Lumsden AB, Ricketts J. Isolated abdominal aortic rupture in a child due to all-terrain vehicle accident—a case report. Vasc Endovasc Surg 2003;37:289-92.

Submitted May 24, 2016; accepted Jul 8, 2016.