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VASCULAR MEDICINE

CASE REPORT: CLINICAL CASE

# Maffucci Syndrome May Be a Heritable Thoracic Aortic Disease and a Cause of Aortic Dissection

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## ABSTRACT

A woman with Maffucci syndrome (MS) presented post partum with type B aortic dissection leading to rupture of a thoracoabdominal aneurysm. Results of multiple-gene testing for heritable thoracic aortic disease were negative. Although conjectural, this patient's aortic disease may be related to MS, and surveillance for aortic disease in patients with MS may be appropriate. (JACC Case Rep. 2024;29:102496) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## HISTORY OF PRESENTATION

A 37-year-old woman with Maffucci syndrome (MS) presented for follow-up of aortic disease initially diagnosed and treated in young adulthood. MS first manifested in this patient at age 4 years, when radiographs of a tibial fracture revealed a large enchondroma. She experienced 39 enchondroma-related fractures in total during childhood, thus leading to a limb-length discrepancy necessitating surgical repair. She developed multiple peripheral cutaneous hemangiomas around the onset of puberty.

### LEARNING OBJECTIVES

- To learn that manifestations of MS include enchondroma, hemangioma, and aneurysm.
- To learn about genetic testing for HTAD syndromes.
- To understand that genetic and imaging screening for HTAD should be considered for patients with MS.

A day after giving birth at the age of 27 years, she stated that she felt a "pop" between her shoulder blades. She presented to the emergency department and was found to have a type B aortic dissection leading to rupture of a thoracoabdominal aneurysm, as diagnosed by computed tomography angiography (CTA). Given the complexity of her preexisting medical comorbidities (see later), she was treated with endovascular stent-graft placement rather than with conventional surgery.

During her intake encounter, most of the patient's concerns were related to comorbidities (discussed later) rather than aortic disease. When questioned

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**ABBREVIATIONS AND ACRONYMS**

**ACC/AHA** = American College of Cardiology/American Heart Association

**CTA** = computed tomographic angiography

**HTAD** = heritable thoracic aortic disease

**MS** = Maffucci syndrome

about her family history, she stated that she was unaware of any family history of heritable thoracic aortic disease (HTAD) and that neither she nor her family members had received any form of genetic screening. She affirmed that she was free of symptoms other than anxiety.

## PHYSICAL EXAMINATION

At her follow-up at age 37 years, the patient's blood pressure was 130/80 mm Hg, and her pulse 80 beats/min. Her musculoskeletal examination findings included firm, nontender, immobile tumors of her right hand, left shin, bilateral shoulders, and pelvis. She had healed amputations of the second and fourth digits of her right foot. A surgical scar was present on the right side of her chest where she once had a tunneled dialysis catheter for end-stage renal disease (removed 1 year after with return to normal renal function). Pertinent negative findings included the absence of pectus abnormality, arachnodactyly, scoliosis, and clubfoot. Her skin examination revealed bluish, compressible, nontender cutaneous nodules of the hands and feet. Pertinent negative findings included the absence of thin translucent skin and atrophic scars. The patient's facial characteristics were noted to be normal. Relevant abnormal findings, such as bifid uvula, hypertelorism, and high palate, were absent.

## PAST MEDICAL HISTORY

In addition to MS and aortic disease, the patient's medical history included cytomegalovirus hepatitis at age 11 years that caused liver failure necessitating liver transplantation. More than 2 decades of immunosuppressant therapy resulted in a host of complications, including multiple infections, thrombocytopenia, anemia, deep vein thrombosis, neuropathy, chronic pain, opioid dependency, depression, and anxiety. At age 25 years, she had a gastric ulcer perforation. At age 35 years, she had renal failure secondary to sepsis that required dialysis; 6 months later, her renal function had returned to normal. Trauma and infection, rather than the musculoskeletal manifestations of MS, led to gangrene and amputations of the second and fourth digits of her right foot.

## DIFFERENTIAL DIAGNOSIS

Most aortic disease occurs in patients of advanced age, with such risk factors as atherosclerosis, smoking, male sex, and hypertension. Genetic disorders such as Marfan syndrome, vascular Ehlers-Danlos syndrome, Turner syndrome, and Loeys-Dietz syndrome, grouped together as HTAD, are direct causes of aortic disease in a young cohort of patients. Infections such as syphilis, tuberculosis, and brucellosis, as well as autoimmune diseases such as Takayasu arteritis and giant cell arteritis are additional rare causes of aortic disease.

**TABLE 1 Genes Tested for 28 Genetic Variants Associated With Heritable Thoracic Aortic Disease[a]**

| | |
|---|---|
| *ACTA2* | *MYH11* |
| *ADAMTS10* | *MYLK* |
| *BGN* | *PLOD1* |
| *CBS* | *PRKG1* |
| *COL3A1* | *SKI* |
| *COL5A1* | *SLC2A10* |
| *COL5A2* | *SMAD2* |
| *EFEMP2* | *SMAD3* |
| *FBN1* | *SMAD4* |
| *FBN2* | *TGFB2* |
| *FLNA* | *TGFB3* |
| *FOXE3* | *TGFBR1* |
| *LOX* | *TGFBR2* |
| *MED12* | *MFAP5* |

[a]Testing included variants associated with Marfan, Ehlers-Danlos, and Loeys-Dietz syndromes. All test results were negative.

## INVESTIGATIONS

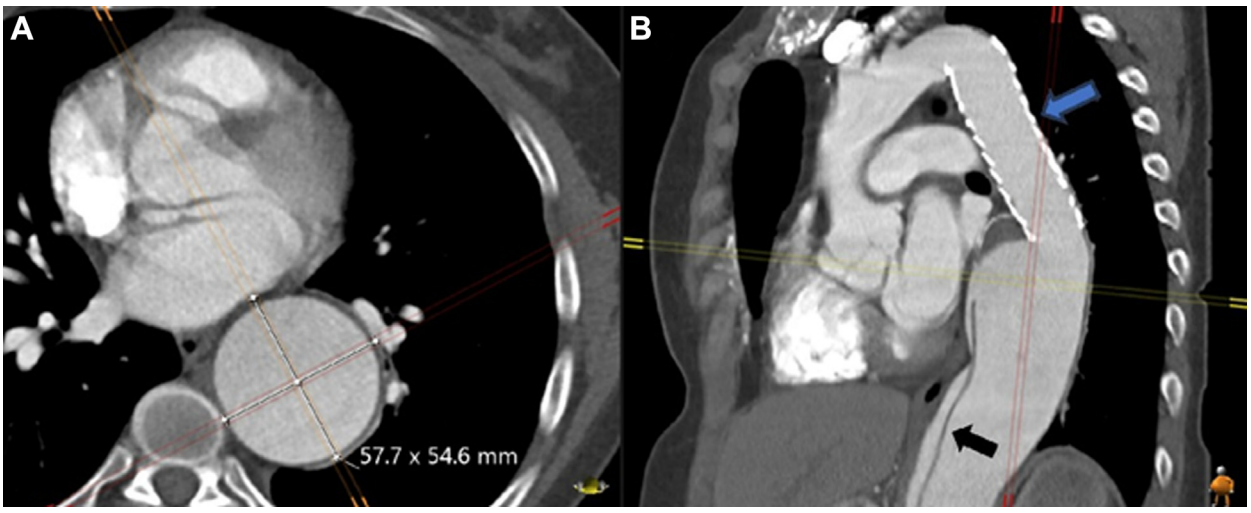
Genetic screening for both syndromal HTAD *(FBN1, COL3A1, SMAD)* and nonsyndromal HTAD *(ACTA2, LOX, PRKG1)* entities was performed, and results were negative on all counts. A complete list of the genes tested is presented in Table 1.

New CTA revealed a residual thoracoabdominal aneurysm 58 mm in diameter with chronic dissection distal to the endograft, and multiple splenic artery aneurysms were also identified (Figures 1A, 1B, 2, and 3). No aortic wall thickening or mural enhancement was present.

## MANAGEMENT

On the basis of aneurysm size criteria (58 mm in transverse dimension), additional aortic repair was advised. Because of her comorbidities (see earlier), endovascular management was recommended rather than conventional surgery. However, the patient declined all surgical options. She accepted recommendations for aneurysm monitoring with serial imaging and aggressive blood pressure control with carvedilol. We counseled her to seek immediate emergency medical care if she experienced symptoms

**FIGURE 1** Multiplanar Reformats of Computed Tomography Angiography Data



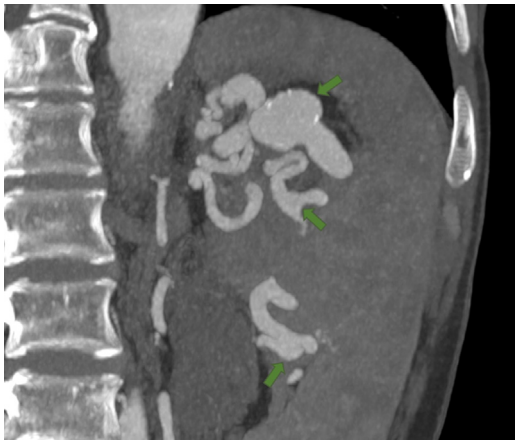

(A) Transaxial dimensions of the aneurysm are 58 by 54 mm (calipers). (B) The endograft (blue arrow) and intimal flap (black arrow) are evident.

of acute aortic syndrome and discussed with her the benefits and risks of imaging and genetic screening for HTAD for her family members.

## DISCUSSION

Genetic disorders that cause weakness of the wall of the thoracic aorta (ie, dissection, intramural hematoma, and rupture) are commonly termed HTAD.[1] HTAD entities often, but not always, have additional phenotypical features, such as pectus abnormality, arachnodactyly, scoliosis, clubfoot, thin translucent skin, atrophic scars, bifid uvula, hypertelorism, and high palate. Conduit artery aneurysms, as were found by CTA in our patient, are common manifestations of HTAD syndromes.[2]

**FIGURE 2** Maximum Intensity Projection of Computed Tomography Angiography Data



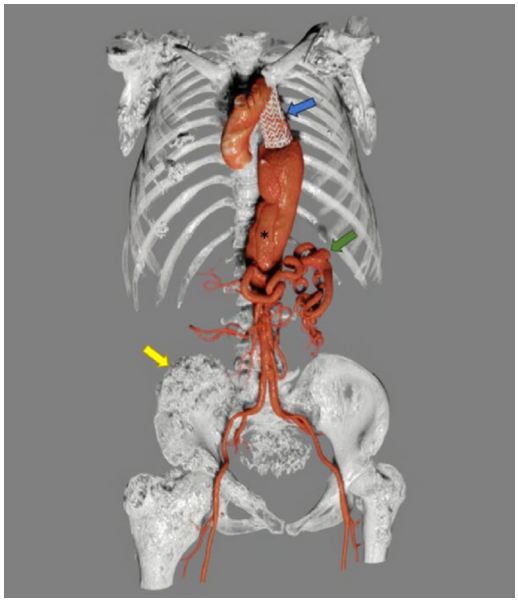
Multiple splenic artery aneurysms (green arrows) are present.

Certainly, our patient with MS would have benefited from imaging screening for aneurysm before her pregnancy. Considering her history of aortic rupture, thoracic aortic endograft placement, still undertreated thoracoabdominal aneurysm with dissection, and splenic artery aneurysms, we hypothesize that she has a form of HTAD.

We recommended imaging and genetic screening for HTAD for the patient's family members. The patient declined this recommendation after expressing concern that testing would result in psychological distress and financial harm for her and her family.

Endograft placement for this patient's acute aortic rupture was a sound choice, particularly given her medical complexity. However, the 2022 American College of Cardiology/American Heart Association (ACC/AHA) guideline for the diagnosis and management of aortic disease recommends conventional surgery for patients with stable HTAD who are at risk of rupture, particularly for patients considering pregnancy.[3] Following this same ACC/AHA guideline, we recommended treatment of her residual aortic aneurysm on the basis of size criteria. Both endovascular and conventional treatments were discussed but ultimately declined.

**FIGURE 3 The 3-Dimensional Rendering of Computed Tomography Angiography Data**



A chronic thoracoabdominal aneurysm with Stanford type B dissection treated proximally with an endograft (blue arrow). The aorta distal to the endograft remains untreated. Note the ribbon-like true lumen of the dissection (asterisk) distal to the endograft. Focal aneurysms of the splenic artery (eg, green arrow) are evident. Multiple enchondromas containing disorganized calcifications (eg, yellow arrow) are seen throughout the skeleton.

MS is a rare, classically nonfamilial mesodermal tissue developmental disease characterized by multiple bilateral enchondromas, secondary skeletal deformities, hemangiomas, and neoplasms both benign and malignant.[4,5] The disease typically manifests during childhood and is dominated by cartilaginous tumors leading to skeletal muscle deformities. Somatic sequence variants have been detected in affected tissues of patients with MS, including variants of isocitrate dehydrogenase 1 and 2, hypoxia-inducible factor 1A, and von Hippel-Lindau tumor-suppressor genes.[5,6]

Although not common, an association between MS and conduit artery aneurysm has been documented in previous studies.[7-9] The negative results of our patient's genetic screening studies, we surmise, indicate that her HTAD-defining sequence variant has yet to be identified. It is conceivable that the somatic mutations in our patient's case caused a spectrum of mesodermal dysplasia that included thoracic aortic disease. We suspect that MS may be a form of HTAD and believe that our patient's unidentified HTAD-defining mutation may be related to her MS. A single case report is far from an association, let alone a proof. However, the alternative explanation, that our patient has not 1 but 2 rare genetic syndromes, we believe to be much less likely. If additional case reports such as ours accumulate in the literature, it may become reasonable to investigate systematically whether MS is a type of HTAD.

## FOLLOW-UP

Close imaging and clinical follow-up, on an every-6-month schedule, were arranged for this patient. A follow-up appointment with the palliative and supportive care service, for management of anxiety related to her complex and serious multiple medical issues, was also scheduled.

## CONCLUSIONS

This case report, although conjectural, raises the possibility of an association between MS and HTAD. By adding to the literature reporting the association of MS with aneurysms in general, it provides incremental evidence that patients with MS have arterial aneurysms generally. A single prepregnancy imaging screen for aneurysms could possibly have benefited our patient, if only it had been performed. Even if based on anecdotal evidence, imaging screening of patients with MS for aneurysm, including thoracic aortic aneurysm, seems a reasonable and prudent consideration.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** **aneurysm, aorta, computed tomographic angiography, CTA, dissection, genetic, heritable thoracic aortic disease, HTAD, Maffucci, pregnancy**