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INTERMEDIATE

CASE REPORT: CLINICAL CASE

Superior Mesenteric Artery Dissection

Classical Presentation, Novel Genetic Determinants

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ABSTRACT

Superior mesenteric artery dissection is a rare cause of acute abdomen. Potential etiologies include atherosclerosis, medial degeneration of the arterial wall, mycotic aneurysm, hypertension, and a variety of arteriopathies. Here, we present a case of superior mesenteric artery dissection prompting clinical genetic testing to investigate the underlying mechanisms of the vasculopathy. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2021;3:690–3) © 2021 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 68-year-old physician presented with 1 day of abdominal pain. On the evening of admission, he suddenly developed right flank pain that subsequently migrated and localized to the right upper quadrant. The pain was associated with nausea and anorexia, but not with fevers, chills, or vomiting. He was subsequently able to sleep but the pain recurred, waking him from sleep at which time he presented to the emergency department at our institution. He denied chest pain, shortness of breath, diarrhea, constipation, dysuria, or hematuria.

At the time of arrival, his temperature was 98°F, his blood pressure was 142/85 mm Hg, and his heart rate was 58 beats/min. His physical examination was normal except for tenderness to palpation in the right upper quadrant, right lower quadrant, and right flank, without rebound tenderness or distension. There were no abdominal bruits. Distal pulses were equal and symmetric in all 4 extremities.

LEARNING OBJECTIVES

- To understand the clinical presentation, risk factors, and management options for superior mesenteric artery dissection.
- To highlight the role of whole-exome sequencing in connecting underlying pathophysiology with unique clinical vascular phenotypes.

PAST MEDICAL HISTORY

His past medical history is notable for monoclonal gammopathy of undetermined significance, esophageal spasm, recurrent *H. pylori* peptic ulcer disease, migraine headache, Raynaud phenomenon, sleep apnea, and prior hepatitis due to cytomegalovirus. His medications prior to presentation included acetaminophen and ibuprofen as needed, nifedipine as needed for esophageal spasm, and ranitidine as needed for gastroesophageal reflex.

His family history is notable for a brother and daughter with Raynaud phenomena, a sister with Sjogren syndrome, ulcerative colitis in his paternal grandmother, and migraine headaches. His mother had Raynaud phenomenon and rheumatoid arthritis. The patient is a physician and lives with his wife. He is also an avid cyclist. He smoked for 3 years in high

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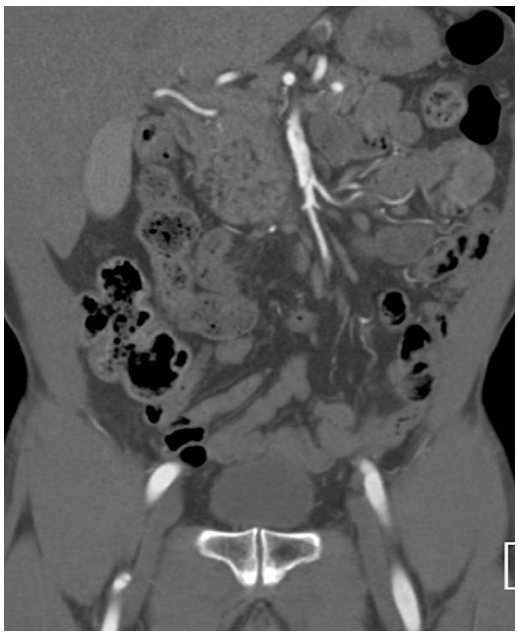
FIGURE 1 Vascular Imaging



Computed tomographic angiography of the abdomen and pelvis shows a 3.0-cm segment dissection of the mid-superior mesenteric artery originating approximately 4 cm from the ostium with mild aneurysmal dilatation

school but has not since that time. He drinks 3 to 4 glasses of wine/week. He does not report any illicit drug use.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for right-sided abdominal pain in this patient includes appendicitis, cholecystitis, nephrolithiasis, pancreatitis, and mesenteric ischemia.

INVESTIGATIONS

Routine laboratory analysis was normal, including the white blood cell count and lipase and lactate levels.

Computed tomographic angiography of the abdomen and pelvis revealed a spontaneous 3.0-cm segment dissection of the mid-superior mesenteric artery originating approximately 4 cm from the ostium with mild aneurysmal dilatation (**Figure 1**). There were no signs of downstream mesenteric ischemia. Aneurysmal dilatation of the right renal artery was also noted, as were the tortuous and ectatic common and external iliac arteries (**Figure 2**).

MANAGEMENT

Based on these imaging findings, he was started on a continuous unfractionated heparin infusion and aspirin 325 mg daily. He had initial resolution of his pain, but on the next day, it acutely recurred. Computed tomographic angiography was again performed, which showed a stable dissection of the mid-SMA. These changes were thought to represent a possible noninflammatory vasculopathy, such as fibromuscular dysplasia or segmental arterial mediolysis. He subsequently underwent magnetic resonance angiography of the brain, which showed no evidence of ectatic arteries or aneurysms.

A work-up for possible vasculitis was initiated with negative serologies for hepatitis B and C, and negative cryoglobulins. Antinuclear cytoplasmic antibodies were negative. Erythrocyte sedimentation rate was 22 mm/h. C-reactive protein was 56.1 mg/l. Kappa free light chain was 21.7 mg/l, and lambda free light chain was 18.4 mg/l with a ratio of 1.18.

CLINICAL COURSE

His pain improved. He was transitioned from unfractionated heparin to apixaban 5 mg twice daily. He was also discharged on aspirin 81 mg daily. Antiplatelet and anticoagulant medications are often used to treat superior mesenteric artery dissection (SMAD) to prevent thrombus and emboli formation, as well as facilitate recanalization of the true lumen (1). It is worth noting that the data supporting their use are primarily observational in nature without rigorous prospective trials (1).

Following his discharge, he had recurrent postprandial pain that prompted readmission. Computed tomographic angiography was unchanged. Given his persistent symptoms, he underwent cephalic vein bypass of his superior mesenteric artery. Pathology revealed cystic medial degeneration and intimal hyperplasia within the SMA aneurysm.

GENOME SEQUENCING

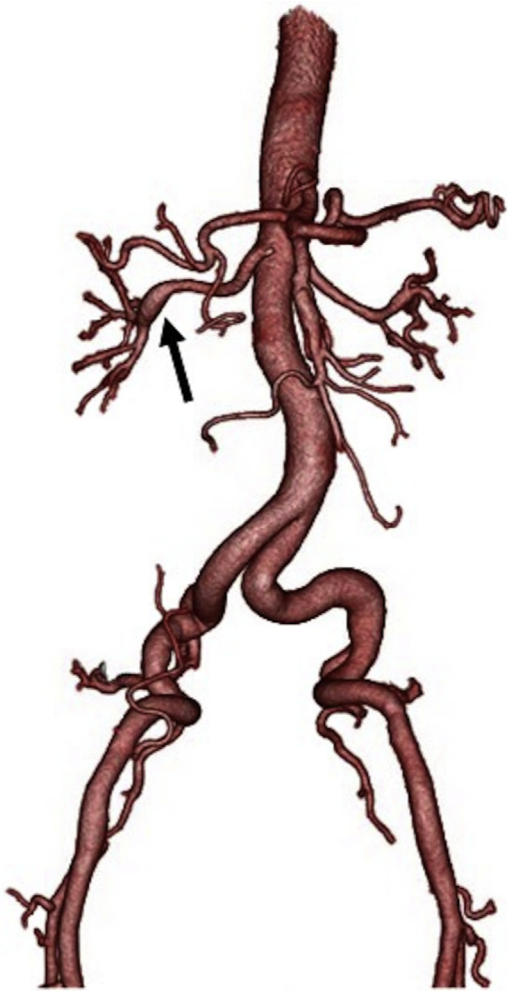
Whole exome sequencing was performed through the Undiagnosed Diseases Network core sequencing laboratory at Baylor College of Medicine for the proband, his brother, his sister, and his maternal uncle (as his father was deceased and his mother unavailable). Two variants of interest were noted: a heterozygous c.332G>A (p.R111H) variant in the *SNIP1* gene, and a heterozygous c.2425C>T (p.P809S) variant in the *COL1A2* gene; the *SNIP1* variant is present in all family members tested, whereas the *COL1A2* variant is

ABBREVIATIONS AND ACRONYMS

SMAD = superior mesenteric artery dissection

TGF = transforming growth factor

FIGURE 2 Vascular Image Reconstruction



A 3-dimensional reconstruction highlighting aneurysmal dilatation of the right renal artery **(arrow)**, and tortuous and ectatic bilateral common iliac and external iliac arteries.

present only in the proband. As this analysis represented a deeper, research-based analysis of the exomes selected to include genes that might be relevant to the patient's phenotype (49 candidate genes), the variants were confirmed by clinical genetic testing using Sanger sequencing. Although these 2 variants are of uncertain significance to pathophenotype, they are both missense mutations that have high probability of loss of function intolerance (pLI) scores. Quantitative mRNA analysis of the patient's fibroblasts revealed no evidence of differential gene expression of these variants compared with wild type.

DISCUSSION

SMAD was first described in 1947 in a case series by Bauersfeld (2). Major complications in the acute stage include arterial rupture and bowel necrosis. More chronically, one can develop aneurysmal dilatation. Conservative management typically includes bowel rest, intravenous fluids, and systemic anticoagulation with heparin. If an individual has persistent abdominal pain, suspicion of bowel necrosis, or progression of the aneurysm, endovascular therapy or vascular surgery can be performed. In one study of 54 patients with SMAD with long-term follow-up (mean duration 18.5 months), 38 patients were symptomatic and 16 were asymptomatic. Only 7 ultimately required endovascular therapy, while the others were managed conservatively (3). A meta-analysis of 727 patients with isolated SMAD found no benefit of treatment with antithrombotic therapy for symptomatic or asymptomatic patients (4).

Populations typically affected include men with a history of atherosclerosis, hypertension, or tobacco use (5). Nevertheless, SMAD should prompt an assessment for arteriopathies, such as fibromuscular dysplasia or segmental arterial mediolysis, as well as interrogation of other arterial beds (6). In one study of 77 patients, 10 patients (13%) had underlying connective tissue disorders (6). Furthermore, patients with angiographic findings suggestive of fibromuscular dysplasia or segmental arterial mediolysis were more likely to require surgical or endovascular intervention (odds ratio: 8.1; 95% confidence interval: 1.002 to 65.889; $p = 0.05$) (6).

Due to the patient's family history of autoimmune connective tissue diseases and vascular phenotypes (migraine, Raynaud) (notwithstanding the lack of evidence of an autoimmune abnormality in the proband and the absence of prior published associations of these disorders with SMAD), and given the unique nature of the phenotype, we enrolled him in the Undiagnosed Diseases Network and obtained detailed whole exome sequencing for him, 2 siblings, and 1 maternal uncle. Two potentially interesting variants were identified for which the patient was heterozygous: c.332G>A (p.R111H) variant in the *SNIP1* gene, and c.2425C>T (p.P809S) variant in the *COL1A2* gene. The *SNIP1* has a high pLI score (0.91), relatively high expression in arteries, and is involved in regulation of

nuclear SMAD2/3 and transforming growth factor (TGF)-beta signaling. TGF-beta signaling has been implicated in Marfan syndrome and Loeys-Dietz Syndrome, both of which are associated with aortic dissection or rupture (7). Similarly, the *COL1A2* has a high pLI score (1.00); medium expression in arteries; and known disease association with osteogenesis imprefecta, Ehlers-Danlos syndrome (arthrochalasis type), and atypical Marfan syndrome. Notably, although the arthrochalasis type of Ehlers-Danlos syndrome is considered a nonvascular subtype, arterial dissections have been reported (8). Although neither of these specific variants has been shown to associate with a definitive pathophenotype, the high pLI score coupled with the mode of inheritance with less severe vascular phenotypes in the proband's relatives (migraine, Raynaud) in the case of the *SNIP1* variant suggests that the patient's vascular presentation may, in part, be explained by his unique digenic genotype. In addition, given the patient's monoclonal gammopathy of uncertain significance, the *SNIP1* variant holds promise because it links TGF-beta signaling and vascular disease with clonal lymphoid disorders. Importantly, there were no changes in the expression levels of the 2 variant genes in the patient's fibroblasts, suggesting that the variants may be functionally important, and in heterozygous combination, contributed to the patient's clinical pathophenotype.

FOLLOW-UP

The patient has been doing well since his revascularization with no further vascular events.

CONCLUSIONS

This case highlights the role of whole exome sequencing in connecting underlying pathobiological processes with challenging clinical cases in vascular disorders.

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