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CERVICAL ARTERY DISSECTION AND ILIAC ARTERY ANEURYSM IN AN SMAD-4 MUTATION CARRIER

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Case report. Cervical artery dissection is an important cause of stroke, especially in younger individuals. Most cases appear to be sporadic, but rare monogenic conditions can cause dissection, such as vascular Ehlers-Danlos syndrome.[1] The wider use of sequencing techniques in clinical diagnosis of genetic disorders has made it more realistic to test for multiple genes in potential monogenic stroke conditions. Here, we report the case of a cervical artery dissection in a *SMAD-4* mutation carrier.

This patient is a 48-year-old man with a history of hypertension, aortic root dilation that led to surgical replacement at age 41, and a subsequent right common iliac artery aneurysm. He had experienced several episodes of mild epistaxis, but none had needed specific treatment. There was no personal history of gastrointestinal symptoms or bleeding.

His family history was suggestive of juvenile polyposis syndrome (JPS). Several colon polyps were diagnosed in his mother; his brother had experienced several episodes of serious digestive bleeding related to multiple colon polyps. The patient has 2 sons and 2 daughters. At age 4, his eldest daughter has had an episode of rectal bleeding that led to the diagnosis of colon polyps; his youngest son has experienced an episode of epistaxis. His youngest daughter and eldest son are doing well.

Physical examination showed slightly translucent chest skin and a possible small telangiectasia in his right cheek. There were no other skin abnormalities; joint examination was unremarkable; heart and neck auscultation was normal.

Because of the aortic and iliac arteriopathy, cerebral CT angiogram was performed to screen for cerebral artery abnormalities. The angiogram revealed 3 findings (figure): firstly, abnormal increased tortuosity of both internal carotids; secondly, mild arterial diameter irregularities; and thirdly, a short but distinct dissection flap in the V2 segment of the right vertebral artery, at the level of C5. The patient had no history of stroke, neck pain, or trauma; therefore, it was not possible to date the dissection. No intracranial abnormality, aneurysm, or arteriovenous malformation was found.

Owing to his multifocal arteriopathy, genetic screening was performed using an arteriopathy gene panel. A heterozygous, loss-of-function, nonsense mutation was found in exon 10 of the *SMAD-4* gene (c.1336C>T; protein change p.Gln446Ter). This Class 4, likely pathogenic mutation, is predicted to create a premature termination codon, resulting in a truncated protein. This mutation has not been identified within in-house databases or in individuals from the Exome Aggregation Consortium project, although a similar c.1333C>T mutation (p.Arg445Ter) has been reported in a patient with JPS, aortic root dilation, and mitral valvulopathy.[2] Segregation studies have been advised to confirm pathogenicity via the Clinical Genetics department.

Discussion. This case illustrates that cervical artery abnormal tortuosity and dissection can occur as part of a systemic arteriopathy due to *SMAD-4* mutation.

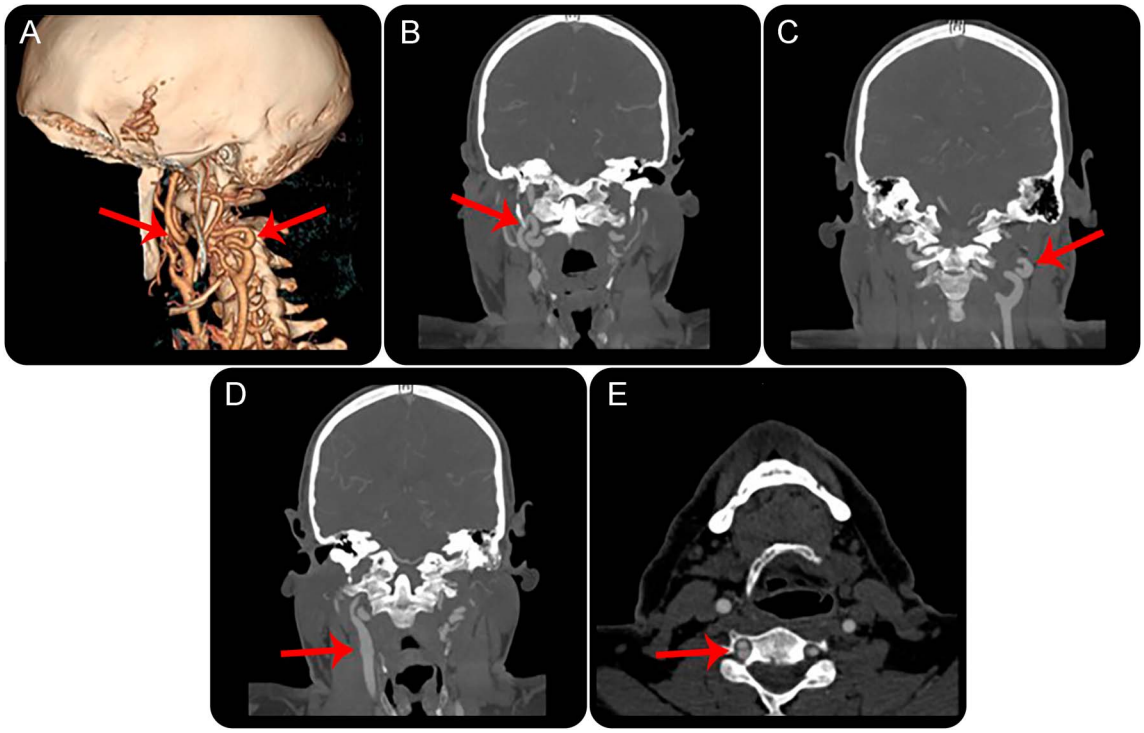
SMAD-4 protein is involved in the transforming growth factor beta signaling pathway. The chromosomal location of the *SMAD-4* gene is 18q21.1. Several *SMAD-4* loss-of-function mutations have been described among patients with JPS and hereditary hemorrhagic telangiectasia (HHT), 2 genetically heterogeneous autosomal dominant disorders.

JPS, occurring in approximately 1/100,000 individuals, is characterized by early-onset colorectal and gastric polyp formation, with a subsequent risk of digestive bleeding, anemia, and malignancy. *SMAD-4* and *BMPR1A* mutations are the most frequently found. The largest JPS series to date has found *SMAD-4* mutations in 21% of cases.[3]

HHT, affecting approximately 1/5,000–10,000 individuals, is a multifocal vascular dysplasia, with skin and mucosal telangiectases and visceral arteriovenous malformations (lung, brain, and liver). Recurrent epistaxis is the most frequent manifestation. The most frequently involved genes are *ACVRL1, ENG,* and *SMAD-4*. Patient series suggest that *SMAD-4* mutations account for 2% of cases.[4] JPS and HHT can be associated in the same individual, usually in case of a *SMAD-4* mutation.

Cardiovascular abnormalities have been described in *SMAD-4* mutation carriers. Thoracic aortopathy

Figure **Cervical artery abnormalities**



(A–C) Abnormal tortuosity of carotid arteries. (D) Mild diameter irregularities. (E) Right vertebral artery dissection flap.

(aortic root dilation) has been reported in 9%–37% of patients[5–7]; heart valve regurgitation in 6%,[5] and intracranial aneurysm in 3%.[5] However, involvement of the cervical and iliac arteries does not seem to be a typical feature of this condition.

This report extends the number of monogenic causes of cervical artery dissection and highlights that *SMAD-4* mutations can cause systemic multifocal arteriopathy, involving not only the aortic root but also the cervical and iliac arteries. Vascular imaging of the arterial tree is advised in at-risk individuals.

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