True radial artery aneurysm in a patient with somatic mosaicism for a mutation in platelet-derived growth factor receptor β gene

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ABSTRACT

We have presented the case of a right radial artery aneurysm (RAA) in a 27-year-old man with cerebral and coronary artery aneurysms and features of Parkes-Weber syndrome (port-wine stains and right upper extremity arteriovenous malformation and overgrowth). The RAA was repaired with an interposition great saphenous vein bypass graft. Analysis of the intracranial artery aneurysm and affected skin demonstrated a somatic mutation in the platelet-derived growth factor receptor-β gene. Mosaicism was present in the RAA but not in the great saphenous vein. Somatic mosaicism should be considered as a possible etiology for peripheral aneurysms in patients for whom standard genetic test results are unrevealing. (J Vasc Surg Cases and Innovative Techniques 2021;7:567-71.)

Keywords: Cerebral aneurysm; Coronary artery aneurysm; Genetic arteriopathy; Platelet-derived growth factor receptor β gene; Radial artery aneurysm; Somatic mosaicism

We have presented the case of a right radial artery aneurysm (RAA) in a 27-year-old man with a history of cerebral and coronary artery aneurysms, features suggestive of Parkes-Weber syndrome (PWS), and a right upper extremity arteriovenous malformation (AVM) to describe the workup undertaken and a novel etiology for the RAA. Details regarding the discovery of the novel pathogenic variant in the present case have been previously reported.[1] The patient provided written informed consent for the report of his case.

CASE REPORT

A 27-year-old man was referred for a right RAA first noted 3 years previously. The RAA was asymptomatic with no history of digit embolization, antecedent trauma, or radial artery access. His medical history included right intracranial carotid artery, right intracranial vertebral artery, basilar artery, and left main coronary artery aneurysms. His surgical history included embolization of an intracranial carotid sacrifice occlusion at the age of 9 years; a right external carotid to middle cerebral artery bypass using the left radial artery, with trapping of the right vertebral artery aneurysm at age 21; and, most recently, a left internal mammary artery to left anterior descending artery bypass and insertion of tandem coated stents between the aorta and circumflex to exclude the coronary artery aneurysm, at age 27 (Fig 1). The left radial artery harvest site was complicated by wound dehiscence. He had undergone multiple procedures with percutaneous femoral artery access without complications. His family history was negative for aneurysms, dissections, or sudden death, and the genetic test results were unrevealing.

His examination demonstrated a pulsatile right RAA (Fig 2). He had a notable upper extremity limb length discrepancy, enlarged right fingers compared with the left, dilated and tortuous forearm veins, and doughy hyperextensible skin over the right elbow. Additional findings (Fig 3) included port-wine stains over the right upper and lower extremities and back, minimal fat deposition in the right lower quadrant, and a large atrophic scar over the right radial artery harvest site.

His upper extremity arterial duplex demonstrated a 1.7-cm diameter and 3.4-cm-long RAA with intraluminal thrombus and an active flow channel of 1.1 cm (Fig 3). The computed tomography angiogram of the neck, chest, abdomen, and pelvis showed no additional aneurysms or dissections. Given the limb asymmetry, notable superficial veins, and port-wine stains—findings matching closest to PWS—a right upper extremity magnetic resonance imaging study was obtained to evaluate for additional vascular anomalies. This demonstrated an extensive high flow AVM with numerous corkscrew-like enlarged veins and cystic lymphatic structures within the subcutaneous tissues along the dorsal and ulnar aspect of the hand, wrist, and forearm (Fig 4). The malformation was fed by the median and ulnar artery branches.

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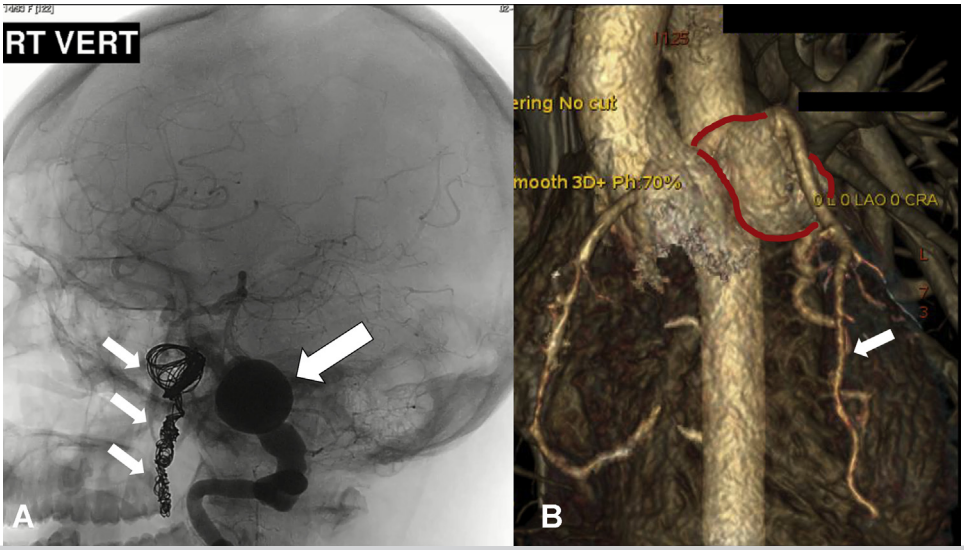

Fig 1. A, Diagnostic cerebral angiogram showing a fusiform aneurysm of the right intradural vertebral artery (*large white arrow*) and no filling of the embolized right internal carotid artery (*short white arrows*). **B,** Distal left main coronary artery aneurysm (*red circle*). The left anterior descending artery (*white arrow*) and circumflex artery arise from the aneurysm sac.

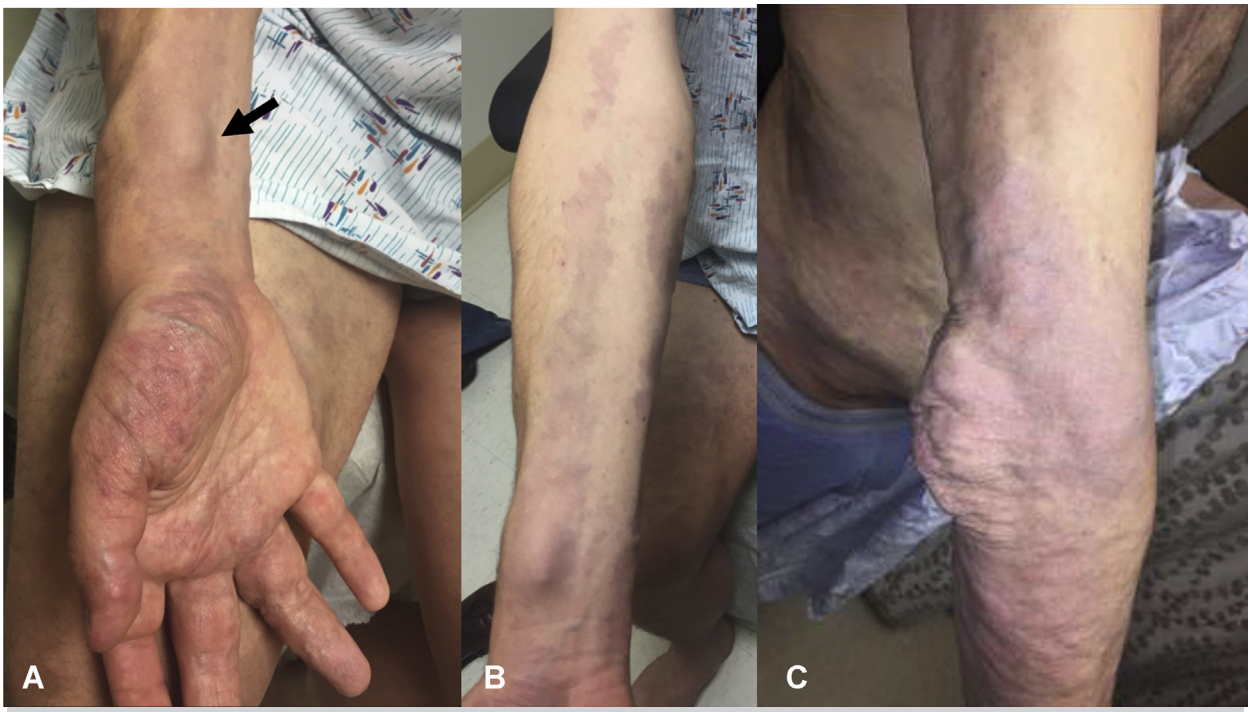

Fig 2. A, Right radial artery aneurysm (*arrow*). **B,** Patchy port-wine stain of the right upper extremity. **C,** Doughy hyperextensible skin overlying the right elbow that extends to the upper and lower arm.

Because the aneurysm and AVM were asymptomatic, he was treated nonoperatively. Subsequently, analysis of tissue from his most recent intracranial artery aneurysm repair detected mosaicism for a single novel c.1685A>G, p.Tyr562Cys, (g.149505130T>C [GRCh37/hg19]) within the platelet-derived growth factor receptor β gene (*PDGFRB*) that was predicted to be pathogenic.[1]

After 2 years of annual follow-up with duplex ultrasound examinations, the patient noted increasing discomfort at the RAA site. Repeat duplex ultrasound showed that the aneurysm had enlarged to 2.2 cm in diameter and 5.5 cm in length with increasing calcification and tortuosity of the radial artery proximally and distally to the aneurysm. He had an incomplete palmar arch with dominant perfusion to the hand by the radial

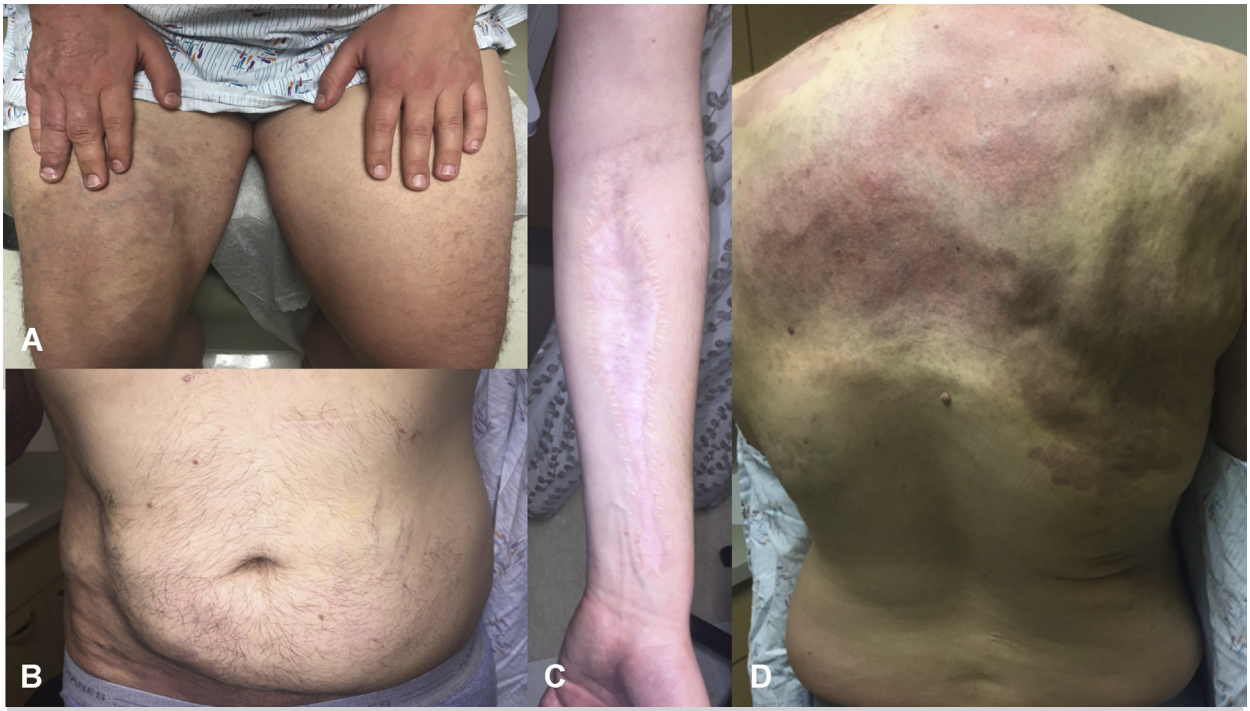

Fig 3. Additional examination findings. **A,** The right fingers were larger than the left. **B,** A lack of adipose tissue was found in the right lower abdomen. **C,** Wide atrophic scarring was present at a previous left radial artery harvest site. **D,** A port-wine stain of the left back.

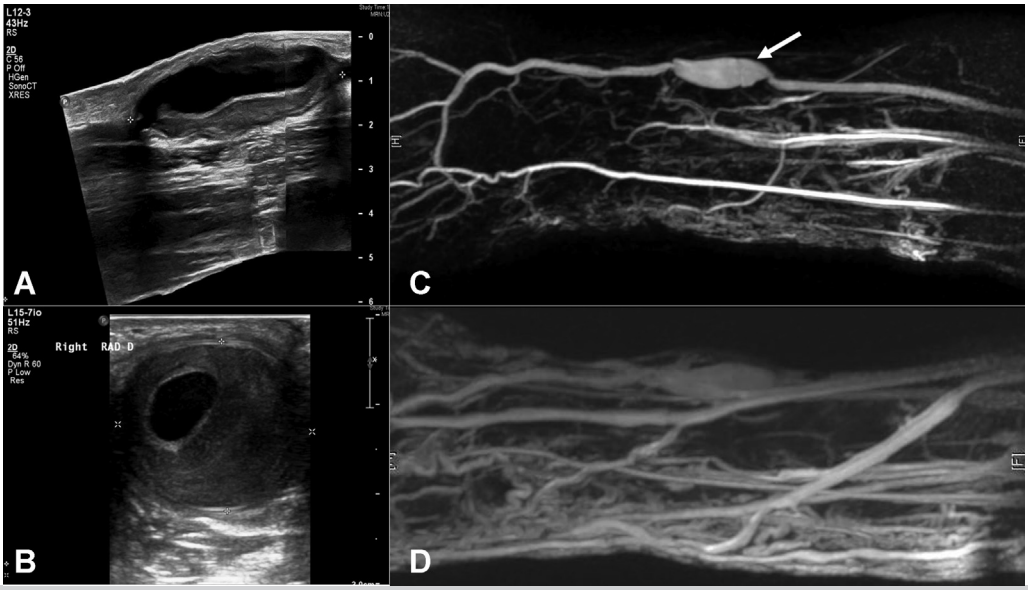

Fig 4. A, Duplex ultrasound scan showing longitudinal view of the right radial artery aneurysm. **B,** Duplex ultrasound scan showing the cross-sectional view of the right radial artery aneurysm (RRA), mural thrombus, and flow channel. **C,** Magnetic resonance angiogram showing the RRA flow channel (*arrow*) and the ulnar artery. **D,** Magnetic resonance venous phase showing the arteriovenous malformation (AVM), which consisted of numerous corkscrew-like, enlarged, rapidly filling veins, with some cystic areas likely representing lymphatic structures within the subcutaneous tissues along the dorsal and ulnar aspect of the hand, wrist, and forearm.

artery. Therefore, the aneurysm was repaired using an interposition great saphenous vein graft harvested from the unaffected left thigh (Fig 5). The postoperative course was unremarkable, and the incisions healed without complications. The same pathogenic variant in *PDGFRB* was identified in the removed aneurysm tissue but not in the great saphenous vein graft. The

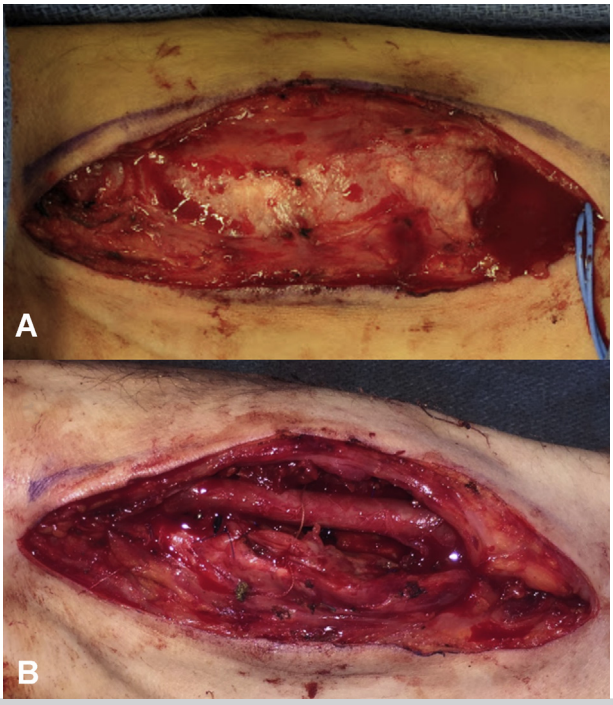

Fig 5. A, Surgical exposure of the aneurysmal segment of the right radial artery in the distal forearm. **B,** Interposition of great saphenous vein bypass graft.

bypass graft remained patent without aneurysmal degeneration or stenosis as assessed by the 1-year postoperative duplex ultrasound examination. However, the patient died shortly after the annual follow-up examination of a ruptured 2-cm midbasilar artery aneurysm with subarachnoid hemorrhage despite the close follow-up.

DISCUSSION

We learned several points from this patient's case. First, somatic mosaicisms that occur after fertilization for pathogenic genetic variants that can control cell growth could be responsible for aneurysms in several different vessels, cutaneous changes, and the development of AVMs. Second, that in some cases, other clinical features can point to the gene in which the alteration occurred. Finally, somatic mosaicism has not been previously described in the setting of peripheral arterial aneurysms, and we should reconsider our thinking about isolated aneurysms and question in each case whether they could represent mosaicism for a mutation in a gene that might influence vessel formation and integrity.

True upper extremity arterial aneurysms are rare, accounting for 1% of all arterial aneurysms.[2] Of those, true RAAs account for a minority of the upper extremity arterial aneurysms.[2-5] The etiologies include idiopathic, autoimmune, hemodialysis access-related, and genetically triggered arteriopathy, such as Marfan syndrome. However, in most cases, the cause will be unknown.[6,7] Operative repair is indicated if the RAA is symptomatic (eg, nerve compression, distal embolization, or rupture, which is exceedingly rare).[2,8] The repair options include bypass graft and ligation.

Somatic mosaicism is the presence of two or more cell populations with different genotypes derived from a single fertilized egg and can occur at different phases of development. Depending on the stage of development in which this occurs, the variant cells can be limited to a portion of the body or widely distributed. This phenomenon occurs in many skin disorders, often with alternating stripes of affected and unaffected skin that follow the lines of Blaschko.[9] This differs from germline variants in which the gene change occurs at the level of the reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring and are heritable.

PDGFRB encodes platelet-derived growth factor-β, which is a cell-surface tyrosine kinase receptor for members of the platelet-derived growth factor family of ligands implicated in complex signaling pathways for cell proliferation, differentiation, survival, and migration. *PDGFRB* is expressed in pericytes and vascular smooth muscle cells and is essential for the regulation of vascular smooth cell proliferation during vascular growth.[10] *PDGFRB* mutations have been associated with primary familial brain calcification,[11] idiopathic basal ganglia calcification,[12] Kosaki overgrowth syndrome,[13] infantile myofibromatosis,[14] dermatofibrosarcoma protuberans,[15] and Penttinen premature aging syndrome.[16]

Our patient's phenotype most closely resembled the rare syndrome PWS, which is caused by mutations in the *RASA1* and is characterized by limb overgrowth, port-wine stains due to capillary malformations, and diffuse AVMs.[17] Before the AVM diagnosis, our patient was thought to have a phenotype similar to that of another rare syndrome, Klippel-Trenaunay syndrome (KTS), characterized by the classic triad of port-wine stains, varicosities, and bone and soft tissue hypertrophy.[18] KTS has been linked to somatic mutations in *PIK3CA*, which encodes a kinase (PI3K) implicated in complex signaling pathways influencing cell growth and division, cell migration, and cell survival.[19] The key to the present patient's diagnosis was the results of the analysis of the cerebral artery aneurysm and abnormal cutaneous tissue.[1] PDGFRB acts upstream of PIK3CA, which might explain the similarity in the present patient's phenotype to that of KTS. Additional work to understand the interplay between these pathways and the observed phenotypes is warranted.

CONCLUSIONS

The present case has illustrated that somatic mosaicism in *PDGFRB* was the etiology for a RAA and upper extremity AVM in a young patient. This finding suggests that somatic mosaicism in *PDGFRB* or other genes could play a role in the etiology of peripheral arterial aneurysms

in patients for whom the standard genetic test results have been unrevealing.

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