

SHORT REPORT

Arteriovenous malformation phenotype resembling congenital hemangioma contains *KRAS* mutations

Christopher L. Sudduth¹ | Anna M. McGuire² | Patrick J. Smits¹ |
Dennis J. Konczyk¹ | Alyaa Al-Ibraheemi³ | Steven J. Fishman² | Arin K. Greene¹

¹Department of Plastic and Oral Surgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

²Department of Surgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

³Department of Pathology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

Correspondence

Arin K. Greene, MD, Department of Plastic and Oral Surgery, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115.
Email: arin.greene@childrens.harvard.edu

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Abstract

Extracranial arteriovenous malformation (AVM) is most commonly caused by a somatic mutation in *MAP2K1*. We report two patients with vascular anomalies that had an unclear clinical diagnosis most consistent with either an AVM or congenital hemangioma. Lesions were cutaneous, reddish-purple with telangiectasias, present at birth, and had defined borders. Histopathology indicated AVM and both lesions contained somatic *KRAS* mutations. A rare AVM phenotype exists that shares clinical features with congenital hemangioma.

KEYWORDS

arteriovenous malformation, congenital, hemangioma, *KRAS*

1 | SHORT REPORT

Extracranial arteriovenous malformation (AVM) is a sporadic, non-hereditary vascular malformation defined by a nidus of irregular blood vessels connecting arteries to veins. Most are caused by somatic mutations in *MAP2K1*,¹ somatic variants in *BRAF*, *HRAS* and *KRAS* also have been identified.^{2,3} We present two patients with an extracranial AVM containing somatic *KRAS* mutations that share clinical features with congenital hemangioma.

The Committee on Clinical Investigation approved this study. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Patient 1 was a 5-year-old male with a 6 cm × 4 cm lesion of the posterior trunk present at birth (Figure 1). The area was asymptomatic and had not changed since birth, except for the recent development of pyogenic granulomas. Physical examination showed distinct borders with a slight peripheral pale halo, pyogenic granulomas, and fast-flow by hand-held Doppler. The differential diagnosis included AVM,

capillary malformation, or a non-involuting congenital hemangioma (NICH). Patient 2 was a 14-year-old male with a well-circumscribed, reddish-purple neck lesion present since birth (Figure 1). The anomaly had remained the same over the patient's life until age 13 years when the component involving the scalp began to enlarge and cause discomfort; the lesion had not previously been treated. Faint pulsations were palpable on exam. The differential diagnosis was AVM or congenital hemangioma [either NICH or rapidly involuting congenital hemangioma (RICH)]. MRI showed a superficial T2 hyperintense lesion with multiple flow voids. Angiography illustrated multiple feeding arterial vessels with early venous drainage consistent with shunting, but less rapid than typically exhibited by AVM. Both lesions underwent serial excision and histopathology was most consistent with AVM. Because the anomalies were atypical for AVM, they were evaluated for somatic mutations. Patient 1 contained somatic *KRAS* mutations by single molecule molecular inversion probe sequencing and droplet digital polymerase chain reaction (ddPCR) (Gln22Lys-mutant allele frequency 4.8%, Gly13Asp-mutant allele frequency 4.5%). Patient 2 was found to contain a somatic *KRAS* mutation by targeted exome sequencing with OncoPanel⁴ and ddPCR (Gly13Arg-mutant allele frequency 33%).

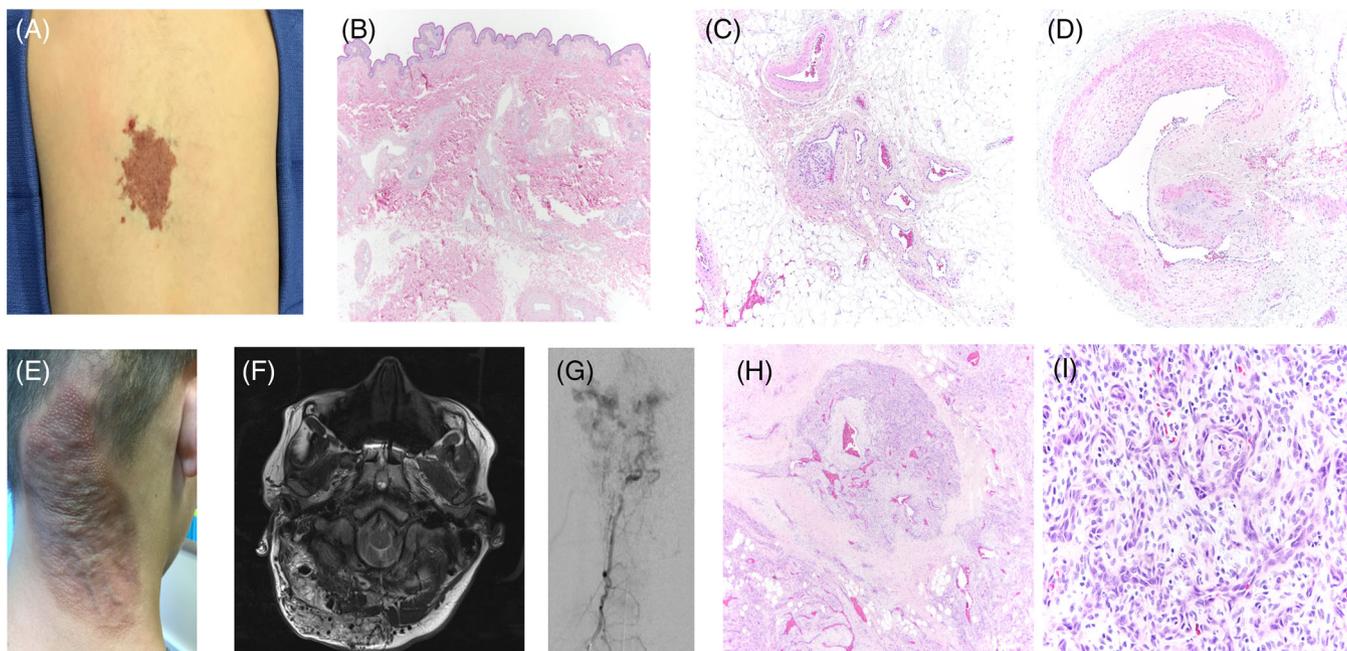


FIGURE 1 A, Posterior trunk of a 5-year-old male (Patient 1) shows a 6 cm × 4 cm somatic *KRAS* (Gln22Lys, Gly13Asp) arteriovenous malformation (AVM) with clinical features similar to a congenital hemangioma. B, C, Histologic examination (hematoxylin and eosin) shows medium to large size channels involving the dermis and subcutaneous tissue [×40 magnification (B), ×100 magnification (C)]. D, Larger channels show intimal fibromyxoid thickening at ×200 magnification. E, Posterior neck of a 14-year-old male (Patient 2) illustrates a somatic *KRAS* (Gly13Arg) AVM with clinical features similar to a congenital hemangioma. F, MRI shows a T2 hyperintense soft-tissue lesion with multiple flow voids. G, Angiography shows a pathological capillary blush with nidus-like architecture and tortuosity of feeding arteries. Venous drainage is early, but less significant than a typical AVM. H, I, Histologic examination (hematoxylin and eosin) demonstrates nodules of small channels, some with capillary morphology and others with thicker, mostly fibrous walls. Channels are separated by fibrous and adipose tissue [×100 magnification (H), ×400 magnification (I)] [Colour figure can be viewed at wileyonlinelibrary.com]

Both lesions clinically appeared similar to a congenital hemangioma, which is a vascular tumor fully-formed at birth. Congenital hemangiomas are reddish-purple, well-circumscribed, exhibit coarse telangiectasias often with surrounding pale rim, and contain somatic mutations in *GNAQ* or *GNA11*.⁵ Unlike AVMs, however, congenital hemangiomas do not have overlying pyogenic granulomas that were present in Patient 1. The lesions of the two patients were able to be differentiated from congenital hemangiomas after histopathological analysis and genetic testing. Histologically, AVMs exhibit large, tortuous arteries, and thick-walled veins. Arteries typically have disruption of the internal elastic lamina with fibromyxoid intimal thickening and hypertensive changes; a small vessel component often is present as well. In contrast to AVM, congenital hemangioma exhibits capillary lobules that can coalesce with one another. The lobular capillaries have plump endothelium with a thin basement membrane surrounded by a layer of pericytes. The endothelial cells may show a hobnail appearance (hyperchromatic nuclei with protrusion into the lumen) with occasional eosinophilic globules in the cytoplasm.

Somatic *KRAS* mutations are the most common cause of intracranial AVMs and in this location do not exhibit a genotype-phenotype correlation.⁶ However, extracranial AVMs containing somatic *KRAS* mutations are associated with atypical AVMs including intramuscular fast-flow vascular anomaly (Lys5Glu, Gly12Asp, Gln22Arg)⁴ and

the congenital hemangioma-like lesions in this report (Gln22Lys, Gly13Asp, Gly13Arg). Extracranial AVM somatic *KRAS* mutations (Gly12Asp, Gly12Val, Gln61His) have been identified in other patients in the literature, but phenotypic associations were not explored.²

A genotype-phenotype correlation is emerging with extracranial AVMs. Most lesions have somatic *MAP2K1* mutations while “atypical” AVMs are more likely to contain somatic *HRAS* or *KRAS* variants. Further mutation identification will continue to delineate congenital vascular lesions and facilitate their diagnosis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support this study are included within the report.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/cge.13833>.

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