Parkes Weber syndrome with lymphedema caused by a somatic 
KRAS variant

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Abstract Parkes Weber syndrome is a vascular malformation overgrowth condition typically involving the legs. Its main features are diffuse arteriovenous fistulas and enlargement of the limb. The condition has been associated with pathogenic germline variants in RASA1 and EPHB4. We report two individuals with Parkes Weber syndrome of the leg and primary lymphedema containing a somatic KRAS variant (NM_004985.5:c.35G > A; p.Gly12Asp). KRAS variants, which cause somatic intracranial and extracranial arteriovenous malformations, also result in Parkes Weber syndrome with lymphatic malformations.

INTRODUCTION

Parkes Weber syndrome is a fast-flow vascular malformation overgrowth condition (Revencu et al. 2008). Its main features consist of diffuse arteriovenous fistulas throughout an extremity, capillary malformation, and limb overgrowth. Arteriovenous shunting can cause a warm limb and congestive heart failure. Treatment includes embolization, excision of overgrown soft tissues, and amputation. Two causes of Parkes Weber syndrome have been identified: germline variants in RASA1 (CM-AVM1) (Revencu et al. 2008) and germline variants in EPHB4 (CM-AVM2) (Amyere et al. 2017). Recently a somatic variant in RASA1 has been shown to cause the condition as well (Flores Daboub et al. 2020).

CASE PRESENTATION

Two unrelated male patients referred to our Vascular Anomalies Center were diagnosed with Parkes Weber syndrome by physical examination, magnetic resonance imaging (MRI), and angiography (Fig. 1). Both subjects had significant left leg enlargement, edema, lymphorrhea, faint cutaneous vascular stains, and repeated infections requiring hospitalization and antibiotic therapy. Neither individual had baseline cardiac overload or a family history of capillary or arteriovenous malformations. Imaging demonstrated diffuse arteriovenous fistulas throughout the leg, subcutaneous microcystic lymphatic anomalies, and lymphedema. Both individuals were negative for germline RASA1 variants (data not shown) and had overgrown skin and subcutaneous tissue excised to reduce the size of their limb.
TECHNICAL ANALYSIS

The resected specimens underwent targeted exome sequencing with OncoPanel (Goss et al. 2019) (Brigham and Women’s Hospital Department of Pathology). The OncoPanel assay surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. The specimen for Patient 1 generated 13,848,235 aligned, high-quality reads with a mean of 302 reads across all targeted exons and 98% of all exons having more than 30 reads. The specimen for Patient 2 generated 8,119,343 aligned, high-quality reads with a mean of 233 reads across all targeted exons and 97% of all exons having more than 30 reads.

RESULTS

Both patient specimens contained a mosaic KRAS variant (NM_004985.5:c.35G > A; p.Gly12Asp) (Table 1). Variant allele fractions were 13% (Patient 1) and 9% (Patient 2).
Droplet digital polymerase chain reaction (PCR) confirmed the variant in the resected tissue of Patient 1 (Patient 2 was not tested) and did not identify the variant in the whole blood DNA of either subject. Testing for EPHB4 variants was not performed.

DISCUSSION

This report shows that KRAS is a locus for Parkes Weber syndrome. Similar to Parkes Weber syndrome caused by germline RASA1 and EPHB4 variants, the individuals had arteriovenous shunting and extremity overgrowth. In contrast, the patients exhibited lymphedema, lymphorrhea, repeated infections, lighter-colored capillary malformations, and significant enlargement of the affected extremity. The same somatic KRAS variant (NM_004985.5:c.35G > A; p.Gly12Asp) recently was reported in a 3-yr-old male with lower extremity overgrowth, arteriovenous fistulas, and capillary malformation; lymphatic dysfunction was not present (Schmidt et al. 2021).

Pathogenic KRAS variants are the most common cause for intracranial arteriovenous malformations (Nikolaev et al. 2018), and most extracranial arteriovenous malformations result from MAP2K1 variants (Couto et al. 2017). Extracranial arteriovenous malformations with KRAS variants are associated with intramuscular fast-flow vascular anomaly (Goss et al. 2019) as well as lesions resembling congenital hemangiomas (Sudduth et al. 2020). Because KRAS variants cause intramuscular fast-flow vascular anomaly, its association with Parkes Weber syndrome, which contains diffuse intramuscular arteriovenous fistulas, is consistent. The association of the KRAS variant with primary lymphedema also has precedent because lymphatic abnormalities can occur in KRAS-related cardiofaciocutaneous and Noonan syndromes (Schubbert et al. 2006; Morcaldi et al. 2015).

Somatic variants in KRAS also have been associated with encephalocraniocutaneous lipomatosis and Schimmelpenning syndrome (Groesser et al. 2012; McDonell et al. 2018). Patients with Schimmelpenning syndrome have an increased risk of vascular anomalies, including lymphatic malformations (Greene et al. 2007). Neither of the patients we describe in this report had clinical findings diagnostic for encephalocraniocutaneous lipomatosis or Schimmelpenning syndrome (e.g., nevus psiloliparus, choristomas, macrocephaly, nevus sebaceous, hypoplastic bones, ocular abnormalities).

This report confirms that Parkes Weber syndrome can be caused by a mosaic KRAS variant. Although Parkes Weber syndrome resulting from RASA1 or EPHB4 germline variants has an overlapping phenotype, KRAS-related Parkes Weber syndrome can also include lymphedema. Individuals with suspected Parkes Weber syndrome without RASA1 or EPHB4 germline variants should be tested for somatic KRAS variants, especially if they exhibit lymphatic malformations. Pharmacotherapy against KRAS or other targets in this pathway might prevent worsening extremity overgrowth.

ADDITIONAL INFORMATION

Database Deposition and Access

The generated data set has been deposited in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) under accession number SCV001739511.
Ethics Statement
The Committee on Clinical Investigation at Boston Children’s Hospital 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.

Author Contributions
W.E. curated the data, administered the project, visualized and conceptualized the project, reviewed and edited the writing, and provided formal analysis, methodology, validation, and investigation; C.L.S., D.J.K., and P.J.S. curated the data, administered the project, visualized the project, administered the software, reviewed and edited the writing, and provided formal analysis, methodology, validation, and investigation; A.H.T. and S.J.F. visualized the project, reviewed and edited the writing, and provided resources, supervision, and validation; A.A. curated the data, administered the software, visualized the project, reviewed and edited the writing, and provided formal analysis, methodology, validation, and investigation; D.M.A. curated the data, administered the software, visualized the project, reviewed and edited the writing, established the methodology, and provided resources, supervision, and validation; and A.K.G. curated the data, administered the project, administered the software, visualized the project, wrote the original draft, reviewed and edited the writing, conceptualized the project, and provided formal analysis, funding acquisition, methodology, resources, supervision, validation, and investigation.

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Competing Interest Statement
The authors have declared no competing interest.

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