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A PEDIATRIC CASE OF *TEK*-RELATED MALFORMATIONS AND MARFANOID HABITUS: AN INCIDENTAL FINDING OR A FEATURE?

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ABSTRACT

Vascular malformations encompass a wide range of complex vascular lesions. Due to the extreme variability of clinical presentation, classification and their related syndromes presents a challenge. Here we describe a case of a boy presenting with Marfanoid habitus, cutaneous vascular malformations, and severe acute anemia due to ileal venous malformations. Although a panel of genetic markers for the Marfan phenotype was negative, we identified a de novo mutation in the TEK *gene in the patient. This case supports expansion of the phenotypic spectrum of* TEK*-related vascular malformations.*

Keywords: vascular malformations, *TEK* gene, pediatric, genetic

Vascular malformations encompass a wide range of complex congenital lesions. These are composed of dysplastic vessels lined by normal endothelium resulting from developmental aberrancies at some stage in the genesis of the vascular tissue. These malformations were in the past distinguished exclusively on the basis of different sets of (major and minor) criteria. Currently, genetic analysis is providing a valuable addition to the classification and offers fascinating new options on the therapeutic ladder (1,2).

CASE REPORT

The patient is a caucasian male. Since the age of 3 months, he developed multiple soft, translucent, and compressible vascular papules that progressively increased in size. At the age of 4 years, he presented severe anemia requiring blood transfusions. A double-balloon enteroscopy with fluoroscopy showed multiple vascular lesions in the small intestine, requiring intestinal resection (*Fig. 1*). Local biopsy showed large ectasic vascular channels of various caliber with areas of thickened vessel walls and phleboliths and immunohistochem-

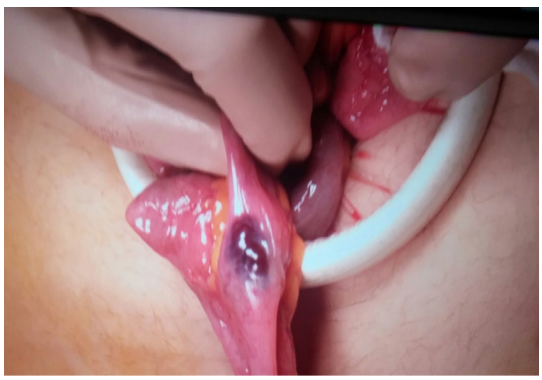

Fig. 1. Inter-operative photograph of vascular lesion in the small intestine of the patient.

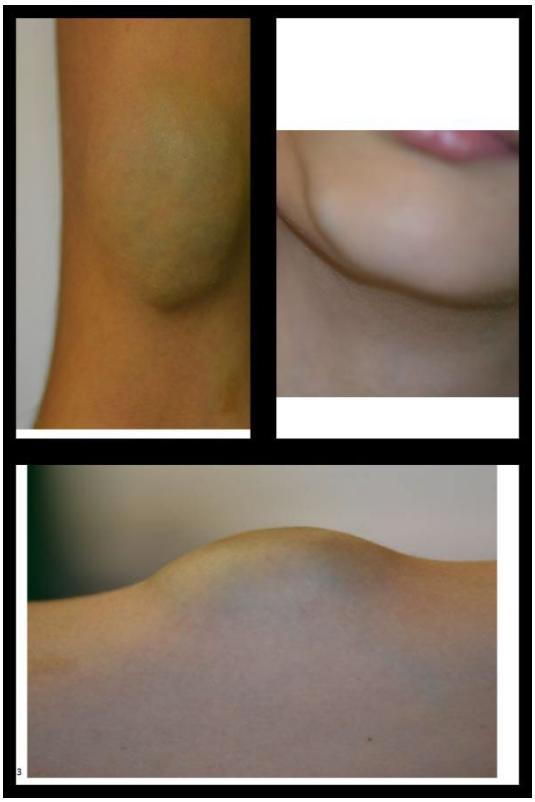

Fig. 2. Photographs of soft, translucent, mobile tumors of the elbow (upper left), chin and jaw (upper right), and arm (lower).

istry revealed CD31+, CD34+, GLUT1- and D2-40-. He was admitted for the first time at our center when he was 12 years old. He presented 3 painless, soft, translucent, mobile tumors (*Fig. 2*) localized in the left elbow (approximately 3 cm in size), right arm (approximately 6 cm in size), and on right chin and jaw (approximately 1.5 cm in size). Complete tumor resection was performed and histological examination showed substantially similar vascular findings surrounded by fibroadipose tissue. Using specific staining (VGFE) the elastic fibers appear reduced and fragmented in the vascular walls on Masson's trichomics.

Long arms, legs, and fingers, tall and thin body, and joint hypermobility were noted. High arched palate, wrist and thumb signs were present (*Fig. 3*). In addition, he showed sternal deformities, and kyphoscoliosis. Ocular and cardiac investigations were normal. He was readmitted to our hospital at 15 yo due to left thoracic pain and shortness of breath. Spontaneous pneumothorax and pneumomediastinum were confirmed by a chest radiograph. We performed NGS Targeted Resequencing analysis on DNA from blood of the patient using a customized panel for genes involved in vascular malformations, identifying a c.2744G>T, p.Arg915Leu (rs387906745) pathogenic variant in *TEK* gene. Family study revealed that this is a de novo mutation which has been reported in the scientific literature (PMID: 19079259) in association with multiple sporadic venous malformations. This mutation was not found in the gnomAD database, two pathogenic alternative variants have been identified (Arg915Cys, Arg915His), and ACMG classifies the variant as PATHOGENIC (class 5).

Fig. 3. Patient demonstrating the thumb sign (top) and Marfanoid habitus (bottom).

DISCUSSION

Due to the extreme variability of clinical presentation, classification of vascular malformations is a challenge, and it has undergone an evolution relying first on histologic findings until the more recent discovery of their molecular basis. The last update of the ISSVA classification (1) reviewed the different forms of vascular anomalies classified as: Common Venous Malformations (CVM, with exclusively cutaneous multifocal venous lesions and/or subcutaneous nodules); familial Venous Malformations Cutaneo-Mucosal (VMCM, involving both skin and mucous membranes); and Blue Rubber Bleb Nevus (Bean) Syndrome (BRBNS, associated to intestinal involvement). TIE2 (TEK) is a Tyrosine-protein kinase that acts as a cell-surface receptor for several angiopoietins (3,4) and is considered causative, in somatic or germinal segregation, in CVM, BRBNS, and Familial VMCM (5,6). However, some clinical entities are still fall outside of this classification. Wouters et al (7) reported 12 new families with VMCM caused by inherited mutations in *TIE2/TEK*, demonstrating a wide range of causative mutations. Cutaneous lesions were mostly located in the cervicofacial region and/or limbs and over 80% of patients had multiple lesions, mostly observed at birth or during the first months of life, as in our patient. In contrast with our experience, symptomatic visceral lesions seem to be uncommon. Shu et al (8) reported VMCM in a Chinese family. All patients had multiple vascular lesions on the oral mucosa and upper and lower extremities. In contrast with our case, only a few lesions were present at birth, while most appeared between 13 and 19 yo. Similar to our patient, Wang et al (9) described a case of BRBNS with a *TEK* mutation presenting with gastrointestinal bleeding. Although a severe gastrointestinal involvement was present in our patient, no rubbery bleb lesions and no palmo-plantar vascular nodules were observed. Boon et al (10) described somatic *TEK*-related entity named "Multifocal venous malformation" characterized by multiple VMs, sometimes associated with gastrointestinal lesions. Recently, the study of Mahajan et al (11) enrolled patients with vascular anomalies and undergrowth, defined as segmental reduction involving the musculoskeletal system. They performed deep high-throughput sequencing in tissue samples using a custom panel and detected two variants in the *TEK* gene in one patient with venous-capillary malformations, and three different variants in the *TEK* gene in the other case. However, the clinical and dermatologic phenotype of their patients is clearly different from our patient.

Marfanoid habitus includes a variety of conditions with phenotypic features that partially overlap the Marfan phenotype including disorders associated with *FBN1/2, TGFBR1/2, COL1A2, COL2A1, COL3A1, COL11A1, PLOD1* mutations. These were all tested in our patient (as well as closely related disorders – *ACTA2, MED12, MYH11, MYLK, SLC2A10, SMAD3, TGFB2, ELN, FLNA*, and *SMAD6*) using specific gene panels and were not found. As far as we know, an association between Marfanoid habitus and *TEK*-related vascular malformations has not been reported yet.

Given the heterogeneity of clinical presentation, at least all venous malformations probably represent a spectrum, varying from mild to severe forms, and Marfanoid habitus is probably somehow linked in our patient despite no known Marfan gene mutations. In conclusion, our observation could further expand the phenotypic spectrum of *TEK*-related vascular malformations (including expansion of the Marfan phenotype), although more cases are required to exclude an incidental association.

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Authors Paola Sabrina Buonuomo and May El Hachem equally contributed to the work.

CONFLICT OF INTEREST AND DISCLOSURE

The authors declare no competing financial interests exist.

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