Verrucous Hemangioma or Verrucous Venous Malformation? Towards a Classification Based on Genetic Analysis

FR - Hemangioma verrucoso o malformación venosa verrucosa? Hacia una clasificación asentada en el estudio genético

N. Knöpfel, a, * P.H. Hoeger b

a Servicio de Dermatología, Hospital Universitari Son Espases, Palma de Mallorca, Islas Baleares, Spain
b Servicio de Pediatría y Dermatología Pediátrica, Katholische Kinderkrankenhaus Wilhelmstift, Hamburg, Alemania

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To optimize investigation in the field of vascular anomalies, it is essential to have an accurate classification system based on a universal, standardized nomenclature. In 1992, the International Society for the Study of Vascular Anomalies (ISSVA) was founded with the goal of standardizing knowledge of vascular lesions among different medical specialists (pediatricians, dermatologists, vascular surgeons, plastic surgeons, radiologists, pathologists, etc.), and its work has contributed to extraordinary advances in scientific understanding in this field in recent years. The ISSVA classification was updated at the April 2014 General Assembly in Melbourne, Australia, but it is recognized in this version that there are still unclassified vascular anomalies. One such example is verrucous hemangioma (Table 1). Imperial and Helwig initially considered verrucous hemangioma to be a vascular malformation involving the subcutaneous tissue with reactive epidermal acanthosis and hyperkeratosis. Its clinical characteristics are similar to those seen in vascular malformations, explaining why certain authors have proposed the terms hyperkeratotic vascular malformation and verrucous malformation to describe this lesion. Verrucous hemangioma, however, has also been classified as a hemangioma, as it has thick-walled vessels, a multilamellated basement membrane, and shows positive staining for WT1 (Wilms tumor 1 protein) and GLUT1 (glucose transporter protein). 2,3

A group of researchers at the prestigious Boston Children’s Hospital of Harvard Medical School recently reported the discovery of a somatic mitogen-activated protein kinase kinase kinase (MAP3K3) missense mutation responsible for verrucous hemangioma, and concluded that this genetic finding strongly supports that this lesion is better designated as a venous malformation. 4 The authors performed whole-exome sequencing in search of somatic mutations affecting the same gene in verrucous hemangioma specimens from 6 unrelated individuals. They found a MAP3K3 missense

* Corresponding author.
E-mail address: nicole.knopfel@gmail.com (N. Knöpfel).
variant (c.1323C>G [p.Iso441Met]), later validated through droplet digital polymerase chain reaction, in 3 of these individuals. Using DNA analysis, they also found the same mutation in 3 out of 4 specimens taken from patients with verrucous hemangioma. This mutation was not observed in the healthy tissue or saliva of affected individuals or in other vascular anomalies, including hemangiomas, capillary malformations, lymphatic malformations, or arteriovenous malformations. The results of this group of researchers are supported by previous studies on mice with global and conditional knockout alleles of MAP3K3 that have shown the implication of this gene in the proliferation and survival of endothelial cells during embryo development.\(^5\) MAP3K3 is involved in the angiopoietin 1 (ANG1) and tunica internal endothelial cell kinase (TIE2) signaling pathway, and the TIE2 pathway has been implicated in both sporadic venous malformations and venous malformations with autosomal dominant inheritance.

In conclusion, the identification of a genetic mutation downstream of the Ang1-TIE2 pathway constitutes a turning point in our understanding of an anomaly that has generated much confusion in the literature. The detection of this mutation confirms that verrucous hemangioma has both clinical and genetic features consistent with a venous malformation, despite the fact that it shows positive staining for WT1 and GLUT1. It also opens the doors for targeted therapy.

### References