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Asymmetric Overgrowth and a Facial Port Wine Stain

A 3-month-old girl presented with generalized marbling of the skin (cutis marmorata) and a striking port wine stain on the philtrum present since birth (Figures 1 and 2). A bilateral sandal gap between the great and second toes (Figure 3), macrodactyly of the left second toe, overgrowth of both feet, hands, and her right leg as well as joint hypermobility were noted. Upon physical and neurologic examination, including measurement of head circumference, no other pathologic findings were observed. Cranial, spinal, abdominal, and hip ultrasound examination, echocardiography, ophthalmologic examination, and otoacoustic emissions testing were unremarkable. Differential diagnosis include infantile hemangioma, Sturge-Weber syndrome, posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies (PHACE) syndrome, Wyburn-Mason syndrome, or a syndrome within the PIK3CA-related overgrowth spectrum (PROS), such as

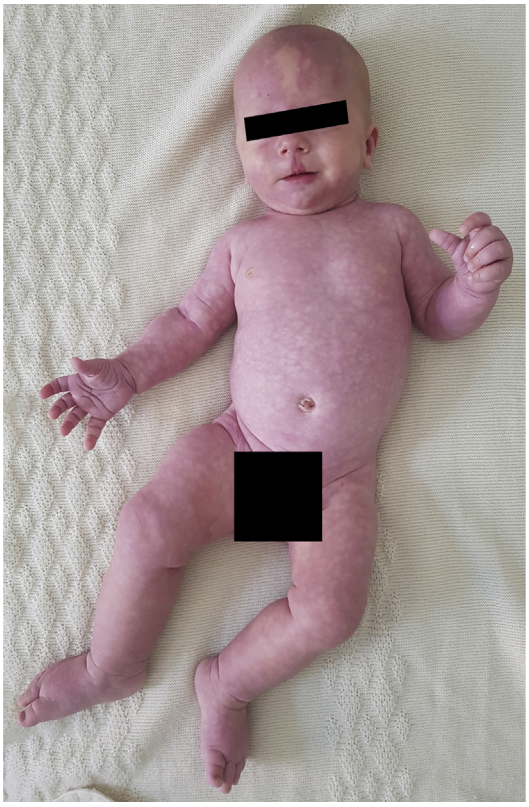

Figure 1. Infant girl with MCAP syndrome at the age of 3 months.

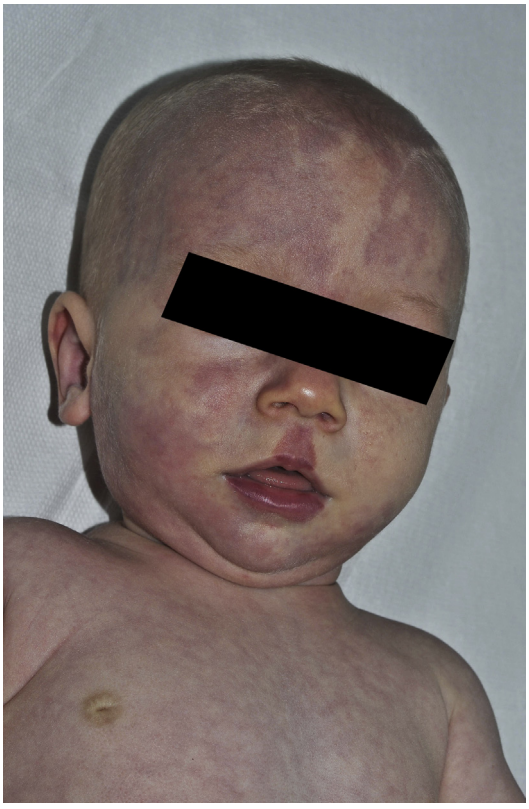

Figure 2. Facial port wine stain at the age of 6 months.

The authors declare no conflicts of interest.

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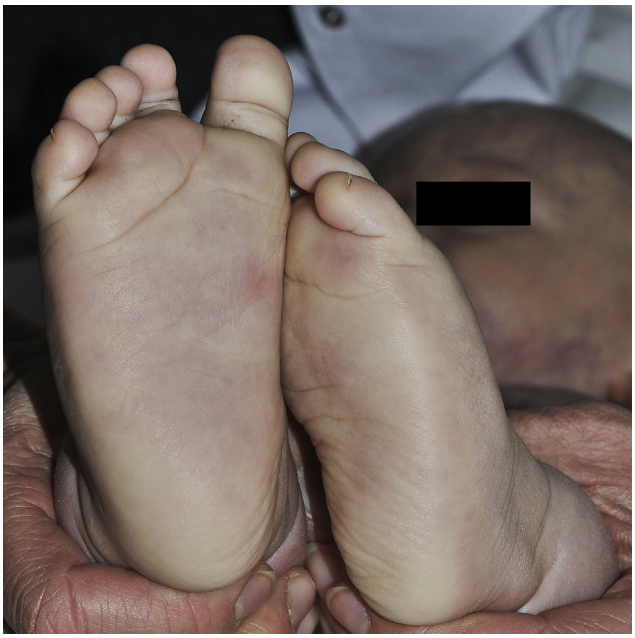

Figure 3. Feet with sandal gap at the age of 6 months.

congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies (CLOVES) syndrome, Klippel-Trenaunay syndrome, or fibroadipose vascular anomaly (FAVA). Genetic analysis of affected skin revealed a somatic mosaic mutation of exon 14 of the PIK3CA gene in 75% of cells, leading to the diagnosis of megalencephaly capillary malformation (MCAP) syndrome.[1] MCAP is a phenotypically heterogeneous entity belonging to PROS.

Somatic mosaicism is defined by the presence of cells with at least 2 different genotypes within one individual, derived from a postzygotic mutation. Somatic mosaic gain-of-function mutations of the PIK3CA gene underly the heterogeneous group of PROS with a broad range of phenotypic manifestations. The spectrum ranges from minor pathologies like small epidermal nevi to severe neurologic, skeletal, or other disorders not compatible with life.[2] Even within the disease entities belonging to PROS, there is a notable heterogeneity of clinical appearance. This finding is underlined by the abscence of megalencephaly but presence of all other typical features of MCAP in our patient. Owing to modern sequencing techniques, the spectrum is constantly extended and characterized more precisely.

There are several promising targeted therapies inhibiting PIK3CA and the related PI3K/AKT pathway like alpelisib and miransertib, known from oncology research.[3,4] Hence, the diagnosis of PROS should be considered in patients with vascular malformations and asymmetric overgrowth. A genetic analysis of affected tissue should be performed to confirm the diagnosis and evaluate availability and potential benefits of targeted therapy. An analysis of unaffected tissue or blood is misleading as PIK3CA mutations are only present in affected tissue at varying levels.[2] Therefore, it might be necessary to obtain more than 1 sample from affected tissue to detect the mutation. Early diagnostic and therapeutic intervention might decrease the severe neurologic, skeletal, and other sequelae of PROS and thus improve the patient's quality of life. ■

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