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Erythematous patches in a female teenager: A novel mutation of *RASA1* in capillary malformation-arteriovenous malformation syndrome type 1

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Abstract

The heterogeneous syndromes caused by germline mutations in genes belonging to the RAS/mitogen-activated protein kinase pathway are often referred to as RASopathies. Abnormal activation of this pathway plays a key role in the development of these disorders. Pathogenic variants in *RASA1* gene cause an autosomal dominant syndrome called capillary malformation-arteriovenous malformation syndrome type 1 characterized by a broad phenotypic variability, even within the same family. In this syndrome, multifocal capillary and arteriovenous malformations are mainly localized in the central nervous system and skin. Herein, we report a patient with capillary malformation-arteriovenous malformation syndrome type 1 with a novel deletion on *RASA1* gene. As this syndrome has been described just over two decades ago, it is most likely underdiagnosed. These kinds of skin lesions, even if unremarkable, should be evaluated by an experienced dermatologist.

Keywords: genodermatosis, vascular malformation, RASopathy

Introduction

In 2003, capillary malformation-arteriovenous malformation syndrome (CM-AVM) was first reported in several families and is characterized by the onset of multiple capillary malformations in childhood [1,2]. It can be associated with internal high flow vascular malformations or arteriovenous malformations, usually in the central nervous system.

It is associated with heterozygous mutations in the RASA1 gene (5q13.3) in type 1, which codes for protein p120RasGAP. Transmission is mainly autosomal dominant, although de novo mutations are found in a third of all cases [3]. Penetrance is usually high, as most patients with the mutation present clinical signs.

Case Synopsis

A 17-year-old girl presented dermatology clinic because of small red patches noted since early infancy. The lesions were not itchy or painful and other symptoms were denied. On physical examination, 6 erythematous homogeneous patches measuring 1cm to 5cm in diameter were observed in multiple locations including the face, neck, back, and dorsal aspect of the hand and forearm. The color ranged from light to deep pink and in some lesions a faint whitish halo could be noticed (**Figures 1A**, **B**) Her medical history was relevant for a preterm diagnosis of congenital cardiopathy with atrioventricular septal defect. In

addition, on fetal magnetic resonance imaging a left thalamic lesion was detected which was attributed to hemorrhagic stroke, although a vascular malformation could not be excluded. She had been followed since childhood by cardiology and neurosurgery consultants and was later diagnosed with epilepsy at age 5 and medicated with valproate. Her father also exhibited similar lesions and was otherwise healthy.

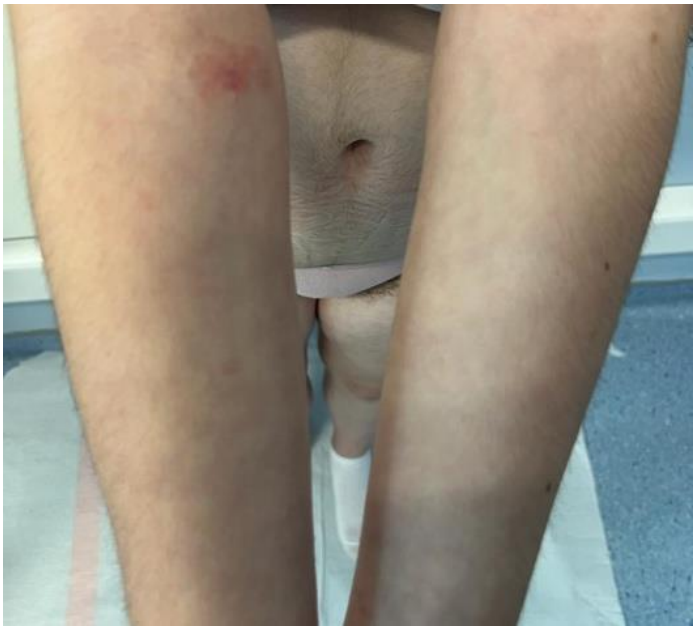

Figure 1A. *Erythematous homogeneous patch on the right forearm. A faint whitish halo is present.*

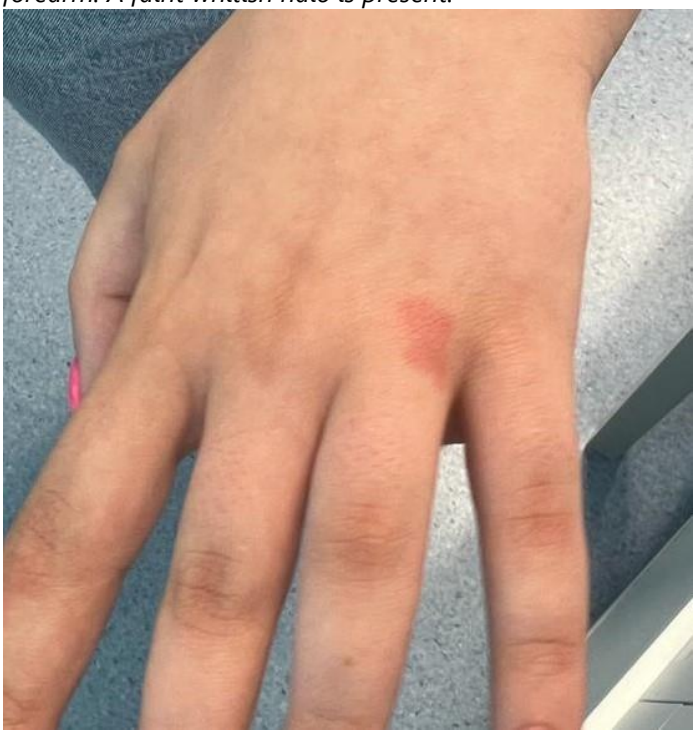

Figure 1B. *Erythematous pink patch on the dorsal aspect of the left hand.*

A 4mm punch skin biopsy was performed on a cervical lesion (**Figure 1C**). The histology demonstrated minimal changes such as mild papillomatosis and capillary ectasia of the upper dermis (**Figure 2**).

A molecular next generation sequencing genetic test was later conducted, revealing a novel heterozygous deletion of exons 14 to 19 on the *RASA1* gene. Such deletion in *RASA1* was assessed in the parents and also present in the father's *RASA1* gene. She was referred for angio-magnetic resonance imaging of the central nervous system which showed a focal area of reduced signal on the superior aspect of the mesencephalic root on the left side, with reduced volume of the left thalamus. This finding was compatible with sequela of probable vascular nature, with a hemorrhagic component.

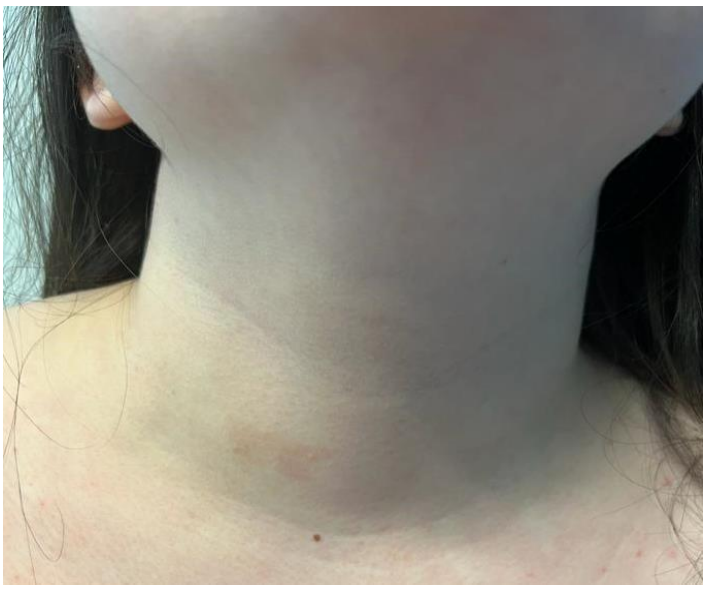

Figure 1C. *Erythematous cervical lesion where the skin biopsy was performed.*

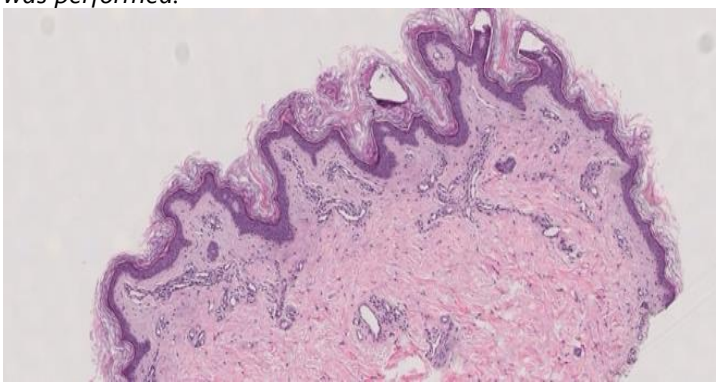

Figure 2. *Hematoxylin and eosin staining at 100x. Minimal changes including mild papillomatosis and capillary ectasia of the upper dermis are present.*

Case Discussion

The multifocal and insidious nature of the lesions in this syndrome may be explained in terms of a "second hit mutation" necessary for development [4]. Over a hundred different mutations in the RASA1 gene have been identified to date. RASA1 is a gene involved in inhibition of RAS-mediated angiogenesis [5]. Indeed, RASA1 encodes a guanosine triphosphate-binding protein activating protein which acts as a negative regulator of the RAS GTPases and the downstream mitogen-activated protein kinase signal transduction pathway [6]. RASA1 haploinsufficiency leads to increased cellular proliferation and survival, mainly in endothelial cells [7].

Clinically, CM-AVM presents in 90% of patients as capillary malformations measuring between 1cm and 3cm in diameter which are pink or occasionally brown, red, or grey and are distributed in a random fashion [8]. A white peripheral halo is seen in around half of these lesions. Although they may be present at birth, they generally appear gradually in childhood, particularly in the first seven years of life.

Even though the RASA1 associated CM-AVM syndrome clinical hallmark appears to be the presence of multifocal capillary malformations, fast-flow vascular malformations are seen in up to a third of affected individuals [9]. The crucial problem in CM-AVM syndrome is this possible association with high-flow vascular malformations, which may be intracerebral and cause symptoms such as headaches, sensorimotor symptoms, and epileptic seizures [10].

Conclusion

We report a patient with CM-AVM syndrome that was diagnosed based on multiple capillary malformations with a novel deletion on *RASA1* gene. As skin lesions were rather inconspicuous, dermatological evaluation was only requested near adulthood. Indeed, the central nervous system sequelae could hypothetically be a result of a central nervous system vascular malformation which caused the epileptic seizures. This case highlights the importance of a thorough medical history and physical examination as well as the value of next generation sequencing genetic testing. Because this syndrome has been characterized only recently, there is a high likelihood of it being underdiagnosed and there will almost certainly be a marked increase in the number of cases reported over the next few years.

Potential conflicts of interest

The authors declare no conflicts of interest.

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