Case Report

Capillary malformation – arteriovenous malformation syndrome (CM-AVM): a diagnosis not to be missed

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Keywords

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Abstract

We present 2 patients with multifocal, small, round to oval, red and pink spots, some with a white halo. The diagnosis of capillary malformation - arteriovenous malformation syndrome (CM-AVM) was made based on their (common) characteristic clinical features and confirmed genetically by documenting a (different) germline heterozygous mutation in the *RASA1* gene. In patients with a genetically confirmed diagnosis of CM-AVM, we recommend that at least one brain MRI angiography be performed at baseline and on a low-threshold basis in individuals with symptoms to rule out intracranial arteriovenous malformations and arteriovenous fistulas.

Introduction

Capillary malformation – arteriovenous malformation syndrome (CM-AVM) is a subtype of capillary malformations, clinically characterized by the presence of multifocal, small, round to oval, pink or red spots, often with a white halo (1).

We present 2 recent cases from our department, in which the presumptive diagnosis was clinically made and genetically confirmed.

Case reports

Case 1

An otherwise healthy 4.5-year-old boy presented with multiple round to oval pink lesions 1-2 cm diameter, some with a white halo, on his face, neck and extremities (Figure 1). Some of these lesions had been present since birth, while others had appeared more recently. Based on the characteristic appearance of these lesions a presumptive diagnosis of CM-AVM syndrome was made.

When this diagnosis was explained to the parents, the 33-week pregnant mother reported having similar lesions on her trunk and extremities (Figure 2).

We performed peripheral blood genetic testing on the boy and his mother and found the same heterozygous nonsense mutation (NM_002890.2): c.2125C>T, p. (Arg709Ter) in the *RASA1* gene in both.

Case 2

A few months later, a 16-month-old boy presented with similar lesions. The pink oval macules on his back and buttocks had been present since birth, whereas the lesions on his arm and knee appeared more recently (Figure 3). Genetic testing documented a heterozygous deletion of 2 nucleotides (NM_002890.2): c.261_262del, p. (Gly89Argfs*22) in the *RASA1* gene.

Discussion

CM-AVM is an autosomal dominant disorder with a prevalence of approximately 1 in 100,000. In the current International Society for the Study of Vascular Anomalies (ISSVA) classification (last updated in 2018), CM-AVM is a subtype of simple vascular malformations (2) (Table 1).

Based on the underlying germline mutation CM-AVM is further subdivided into CM-AVM1 with a mutation in the *RASA1* gene (50% of cases) and CM-AVM2, caused by a mutation in the *EPHB4* gene (25% of cases) (3). On top of the germline mutation, a somatic "second hit" is required for the disease to develop. This explains the high inter- and intrafamilial clinical variability and the variable penetrance (1,4,5).

Both CM-AVM1 and CM-AVM2 are characterized by the presence of multifocal, small, round to oval, pink or red macules, often with a white halo. Some of these capillary malformations are already visible at birth, while others appear during the next few years of childhood.

However, CM-AVM1 and CM-AVM2 differ in some aspects. Annular lesions, lip telangiectasia, and Bier spots are found only in CM-AVM2, while associated fast-flow vascular malformations are more common in CM-AVM1 (10% of cases) than in CM-AVM2 (3% of cases). These fast-flow vascular malformations include intracranial and extracranial AVM, AVF and Parkes-Weber syndrome. Symptoms of intracranial AVM/AVF can occur already early in life, with life-threatening complications including hemorrhage, congestive heart failure, and neurological consequences.

In both cases presented here (and in the mother of case 1), MRI angiography of the brain and spine excluded the presence of intra- and extracranial AVM and AVF.

Recently ultrasound examination showed that CM in CM-AVM syndrome are also fast-flow lesions, suggesting that the capillary malformations in CM-AVM should be considered as pre-AVM. This implies that CM-AVM syndrome will have to be classified differently in the next ISSVA classification.

In the differential diagnosis, the skin lesions may be confused with other macular skin lesions such as café-au-lait macules and cutaneous mastocytosis. Other syndromes with cutaneous vascular malformations include Klippel-Trénaunay-Weber syndrome, Parkes-Weber syndrome, hereditary hemorrhagic telangiectasia (HHT, Rendu-Osler-Weber syndrome), and Sturge Weber syndrome (6).

The presumptive clinical diagnosis should be confirmed by genetic testing of the patient and any at-risk family members. Routine performance

Table 1: ISSVA Classification 2018| International Society for the Study of Vascular Anomalies (2).

Simple vascular malformations	Causal gene
Capillary malformations (CM)	
Naevus simplex (aka "salmon patch", "angel's kiss" and "stork bite")	
Cutaneous and / or mucosal CM (aka "port-wine" birthmark)	
Nonsyndromic CM	*GNAQ*
CM with CNS and /or ocular anomalies (Sturge-Weber syndrome)	*GNAQ / GNA11*
CM with bone and / or soft tissue overgrowth	*GNA11 / PIKCA / HRAS / PIK3R1 / AKT*
Diffuse CM with overgrowth (DCMO)	*GNA11 / PIK3CA*
Reticulate CM	
CM of MIC-CAP (microcephaly-CM)	*STAMBP*
CM of MCAP (megalencephaly - CM - polymicrogyria)	*PIK3CA*
CM of CM-AVM	*RASA1 / EPHB4*
Cutis marmorata telangiectatica congenita (CMTC)	*GNA11*
Telangiectasia	
Hereditary hemorrhagic telangiectasia (HHT)	*ENG / ACVRL1 / SMAD4*
Others	

of MRI angiography of the brain and spine is still a matter of debate. However, based on recent research documenting the potential life-threatening complications of associated AVM and AVF early in life, we recommend that brain MRI be performed at baseline and repeated in symptomatic individuals (7).

Treatment depends on the clinical manifestation of CM-AVM. For CM and telangiectasias that are only of cosmetic concern the patient may be referred to a dermatologist for pulsed dye laser treatment. For associated AVM or AVF, the risks and benefits of intervention must be considered, with embolization and surgery being the 2 interventional options. If the patient experiences cardiac overload, referral to cardiology required. For hemihyperplasia and/or leg-length discrepancies an orthopedist may be consulted, and an otolaryngologist for epistaxis.

Conclusion

In both cases presented here the diagnosis of CM-AVM was made on the basis of their (common) characteristic clinical features, and confirmed genetically, documenting a (different) germline heterozygous mutation in the *RASA1* gene. In patients with a genetically confirmed diagnosis of CM-AVM we recommend that at least a brain MRI be performed at baseline and on a low-threshold basis in individuals with symptoms to exclude intracranial AVM and AVF.

Conflict of interest

The authors have no conflict of interest to declare.

Financial support

There was no external funding.

Informed consent

Informed consent was obtained from both patients.

Figure 1: 4.5 year old boy with small, round to oval, pink macules on the face, neck, trunk and extremities.

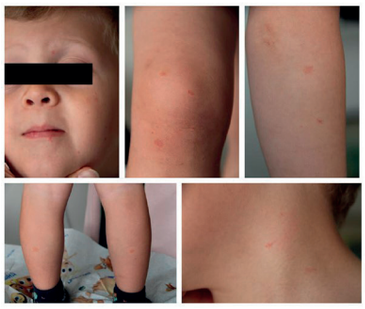


Figure 2: Mother of the 4.5 year old boy with round to oval, pink macules on trunk and extremities.

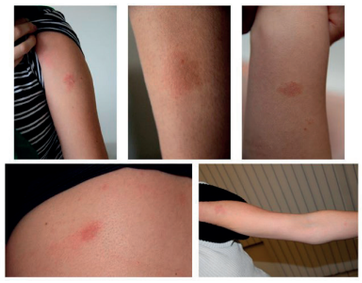
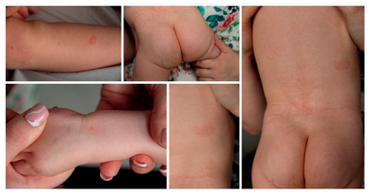


Figure 3: 16-month-old boy with pink macules on back, buttocks and extremities.



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