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Case Report

What Can It Be If Not a Simple Haemangioma?

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Abstract Capillary haemangioma is a common dermatological condition, which present in approximately 1-2% of infant. While 30% appear at birth, almost all will be apparent by the age of 6 months. Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is an autosomal dominant disorder that characterised by the presence of multiple small capillary malformation, formation of high flow vascular anomalies like arteriovenous malformation (AVMs) and / or arteriovenous fistulas (AFVs) which typically develop in skin, muscle, brain, spine and rarely in bone. The prevalence is about 1:100,000.[1] Despite its rarity, it is still an important disease to recognise and differentiate from simple capillary haemangioma. As CM-AVM syndrome may lead to life threatening complications like congestive heart failure, rupture of AVM especially intracranial lesion which may leads to devastating neurological consequences. Here we present the first reported case of *RASA1* related CM-AVM syndrome in Chinese, discuss on its clinical features and differential diagnosis, together with the indication for genetic referral.

Key words Capillary haemangioma; Capillary malformation-arteriovenous malformation syndrome; CM-AVM; *RASA1*

Case Report

A 2.7 kg female baby was born at 35+5 week of gestation. Antenatal ultrasound at 34 week of gestation showed features of hydrops fetalis. Upon delivery, she was noted to have generalised lymphoedema with bilateral chylothorax, which resolved and stabilised after drainage and octreotide treatment. Echocardiogram showed normal cardiac structure. Other investigations for hydrops included congenital infection screening, microarray and Karyotyping were all negative. Family history was unremarkable. A haemangioma was developed at the left angle of mouth since age of 1 month old. She was first seen in our genetic clinic at 4 months of age for subtle dysmorphic features and perinatal history of hydrops fetalis. Physical examination at 4 months old showed she had body weight of 5.8 kg (10th centile), body length 63 cm (25-50th centile) and head circumference of 40 cm (10th centile). A capillary haemangioma was noted at the left angle of mouth. There was subtle dysmorphic features included hypertelorism, downslanting palpebral fissure, depressed nasal bridge and low set posteriorly rotated ears (Figure 1). The clinical diagnosis of Noonan syndrome was initially made. Genetic testing for RASopathy included *PTPN11, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, RAF1, RIT1, SHOC2* and *SOS1* genes were all negative. On subsequent follow up, there was gradual progression of the haemangioma that extending to the gum which resulted in dental malocclusion (Figure 1). Another 2x3 cm paraspinal subcutaneous haemangioma was also noted and confirmed by ultrasound at 1 year old. MRI brain and head with contrast

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at 3 years old showed a haemangioma with underlying high flow vessels within the subcutaneous fat over left angle of mouth. No arteriovenous malformation detected in brain parenchyma. She got mild developmental delay but catched up with training. In view of the above vascular malformation phenotype, capillary malformation-arteriovenous malformation (CM-AVM) syndrome was suspected and *RASA1* {NM_002890.2} gene sequencing was performed. A de novo heterozygous one base pair deletion c.482delG in exon 1 of *RASA1* gene was detected. The molecular diagnosis of *RASA1* related CM-AVM syndrome was substantiated. This was also a novel mutation in the literature.

Discussion

Familial multiple capillary haemangioma and/or AVM has been described for many years and the genetic locus was firstly mapped to chromosome 5q by Breugem et al[2] and Eerola et al[3] in 2002. In subsequent year, *RASA1* mutation was identified to be the cause of CM-AVM and Parkes-Weber syndrome which have CM-AVM and soft tissue or skeletal hypertrophy of the limbs.[4] The underlying pathophysiology of *RASA1* mutation that lead to vascular malformation are remained to be elucidated. But it is proposed that *RASA1* encoded for p120-RasGTPase-activating protein (p120-RasGAP), which negatively regulated the Ras/MAP-kinase pathway. Ras/MAP-kinase pathway is important for endothelial cells development. Therefore, dysregulation of *RASA1* function would result in abnormal microvascular networks formation.[5,6] With highly selected patient with CM-AVM, the diagnostic yield of *RASA1* testing is around 50-60%.[7]

Typical features of CM-AVM is the presence of CMs (98.5%) which mainly found on skin and rarely on mucosa. Majority of them (97%) will have multiple cutaneous lesions. Most CMs are round or oval shape in pink colour

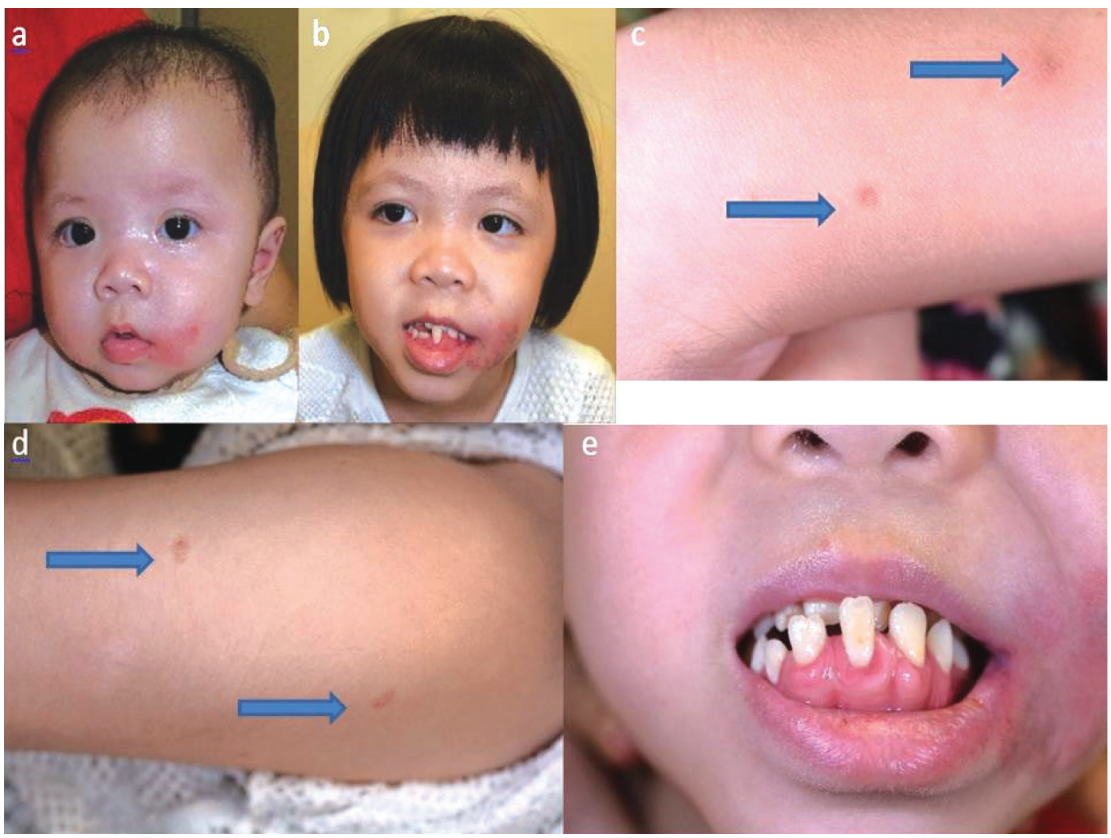

Figure 1 (a) and (b) Evolving of left jaw haemangioma at the age of 5 months and 3 years old respectively. (c) and (d) Multifocal capillary haemangiomas with characteristic halo (blue arrows) over the upper arms. (e) At age of 6 years old, the vascular malformation over the left angle of mouth has extended into oral cavity that lead to gum swelling and dental malocclusion. (Consent for publication has been obtained).

and some have characteristic surrounding halo. Majority of them are present at birth and increased in size and number gradually. About 60% of patients have fast flow vascular malformation. These AVMs and AVFs are mainly located on the extremities, intracranial (25%), intraspinal (15%), head and neck region (21%). About 5% will present with features of Parkes Weber syndrome. AVMs and AVFs may present in neurological symptoms if located intracranially or intraspinally that include seizure, migraine or stroke. Large fast flow vascular malformation could also complicate with congestive heart failure. Non immune hydrops have rarely reported for CM-AVM.[8]

Differential diagnosis of *RASA1* related disorder include hereditary haemorrhagic telangiectasia, Klippel Trenaunay syndrome, Sturge Weber syndrome, PTEN hamartoma tumour syndrome, multiple cutaneous and mucosal venous malformations, hereditary glomuvenous malformations. Clinical presentation of the above entities and their distinguishing features from *RASA1* related disorder are summarised in Table 1.

Capillary haemangoima and port wine stain are extremely common in paediatric population, with a birth incidence of 1-2%. Identification of *RASA1* related disorder is important as it may associated with potential sinister and life threatening complications. Therefore, we proposed several indications for referral to dermatologist or clinical geneticist. It includes

1. presence of multifocal, atypical pink to reddish brown, round to oval lesion, with or without a halo surrounding the lesion;
2. the presence of arteriovenous malformations (AVMs) or arteriovenous fistulas (AVFs) in soft tissue, bone and brain;
3. the presence of soft tissue and bony overgrowth, which may point to the diagnosis of Parkes Weber syndrome;
4. the presence of positive family history.

Regarding for the management of CM-AVM, baseline brain and spinal imaging is recommended after the initial diagnosis to look for AVMs and AVFs. However, there is no consensus for the subsequent radiographic evaluation. Referral to dermatologist for assessment and follow up is

Table 1 Differential diagnosis of *RASA1* related disorder

	Gene involved	**CMs**	**AVM**	**Soft tissue overgrowth**	**Distinguishing features from *RASA1* related disorder**
Hereditary haemorrhagic teleangiectasia	ENG ACVRL1 SMAD4	–	+	–	- Characteristic lip or tongue telangiectasia - AVM in liver or lung - Epitaxis and abnormal vessels in mucosa is common - GI bleeding
Sturge Weber syndrome	GNAQ	+	–	–	- Facial cutaneous vascular malformations over ophthalmic branch of trigeminal nerve - Seizures - Glaucoma
Klippel Trenaunay Weber syndrome	PIK3CA	+	–	+	- Vascular malformations are typically low-flow lesions without high-flow AVMs
PTEN hamartoma tumour syndrome	PTEN	–	+	+/-	- Vascular anomalies are usually intramuscular, are associated with ectopic fat, and severely disrupt tissue architecture - Tumour predisposition (breast and thyroid cancer) - Macrocephaly - Papillomatous papules
Hereditary glomuvenous malformations	GLMN	+	–	–	- Hyperkeratotic, raised and nodular with a cobblestone surface - Bluish purple in colour
Multiple cutaneous and mucosal venous malformations	TEK	+	+ (especially involving muscle)	–	- Small, multifocal bluish cutaneous or mucosal venous malformations - May invade subcutaneous muscle & cause pain

also recommended. Embolisation or surgical treatment may be occasionally needed depending on the size and location of the AVMs and AVFs. Furthermore, it is important to watch out heart failure symptom. For Parkes Weber syndrome, input from orthopedic surgeon would be necessary. Finally, genetic counselling is important. Prenatal diagnosis and family planning issues can be addressed during the consultation.

In summary, we report the first case of *RASA1* related CM-AVM syndrome in Chinese that present initially with hydrops fetalis with subsequent multiple cutaneous capillary haemangioma. Increase in clinical awareness of this disease entity is important due to the possibility of associated devastating complications.

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Declaration of Interest

None

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