

## Beyond Hereditary Haemorrhagic Telangiectasia (HHT): Capillary Malformation–Arteriovenous Syndrome (CM-AVM)

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### Abstract

#### *Presentation*

A woman in her forties, asymptomatic, was referred to the respiratory clinic with suspected HHT due to mucocutaneous telangiectasia involving her face, lips, and hands. Auscultation revealed an audible bruit over her left posterior chest wall.

#### *Diagnosis*

MRI brain and spine showed no evidence of cerebral arteriovenous malformations. Genetic testing identified a heterozygous EPHB4 splice variant consistent with CM-AVM syndrome. It was negative for mutations associated with HHT.

#### *Treatment*

Red flags indicating pulmonary, intracranial or spinal haemorrhage were explained to the patient. She was linked in with the HHT clinic for routine follow-up and received genetic counselling.

#### *Discussion*

CM-AVM is a rare autosomal dominant vascular malformation syndrome that can clinically mimic HHT but is genetically and phenotypically distinct. It should be considered in patients presenting with mucocutaneous vascular lesions. Genetic testing is essential to guide appropriate surveillance, management, and genetic counselling.

### Introduction

Capillary malformation-arteriovenous syndrome (CM-AVM) is a rare genetic disorder characterised by capillary and arteriovenous malformations as well as arteriovenous fistulas (AVFs). It is similar to hereditary haemorrhagic telangiectasia (HHT) but rarer, occurring in 1 in

100,000 of the population. It is inherited in an autosomal dominant fashion. Unlike hereditary haemorrhagic telangiectasia, CM-AVM typically presents with congenital capillary malformations and fast-flow AVMs or AVFs, often in childhood, and lacks the recurrent epistaxis characteristic of HHT. Genetic distinction is also clear, with CM-AVM associated with *RASA1* or *EPHB4* mutations rather than the *ENG* or *ACVRL1* variants seen in HHT.

### **Case Report**

We present the case of a woman in her forties, referred to the respiratory clinic by her GP with suspected HHT given red spots on her face and lips. She is an ex-smoker with a history of vertigo and takes no regular medications. The patient reported no relevant medical conditions in the family. At ten years old, her dentist noted cutaneous telangiectasias and suggested a potential diagnosis of HHT.

On examination, she had multiple areas of mucocutaneous telangiectasia on her face, lips and hands. Auscultation revealed an audible bruit over her left posterior chest wall.

Echocardiogram was unremarkable. MRI of the brain showed greater than expected white matter changes for her age, with no evidence of cerebral arteriovenous malformations (AVMs). MRI whole spine was also negative for AVMs.

To complete her work-up, genetic testing was negative for mutations associated with HHT. However, it did identify a heterozygous *EPHB4* splice variant. Given the patient's clinical picture, this is diagnostic of CM-AVM.

Red flags for a possible pulmonary, intracranial or spinal haemorrhage were explained to the patient. In the case of acute presentation, urgent imaging would also be required. She was linked in with the HHT clinic for routine follow-up and received genetic counselling.

### **Discussion**

CM-AVM is a rare autosomal dominant vascular malformation disorder caused by mutations in *RASA1* (CM-AVM1) or *EPHB4* (CM-AVM2), which lead to the disruption of RAS–MAPK signalling that is critical to vascular development<sup>1,2,4</sup>. It typically manifests in childhood with multiple congenital capillary malformations (CMs) but can also be associated with fast-flow arteriovenous malformations (AVMs) or fistulas (AVFs) affecting skin, muscle, bone, brain, or spine<sup>1,2,5</sup>.

It is similar to HHT, as both syndromes share overlapping clinical features such as mucocutaneous vascular lesions and risk of AVMs. However, unlike HHT, where recurrent

epistaxis is a hallmark and visceral AVMs (particularly pulmonary and hepatic) are common, CM-AVM patients usually lack significant haemorrhagic epistaxis and do not routinely develop pulmonary or hepatic shunts<sup>1,3,5</sup>. Genetic testing is central to differentiating these disorders. Panels usually include *RASA1* and *EPHB4* alongside *ENG*, *ACVRL1*, and *SMAD4*. In CM-AVM, identification of a pathogenic *EPHB4* variant, as in this case, confirms the diagnosis in the absence of HHT-associated variants.

Management of CM-AVM focuses on appropriate surveillance for fast-flow lesions. Brain and spinal imaging at diagnosis is recommended to identify treatable AVMs/AVFs before symptoms develop, with repeat imaging guided by new clinical signs<sup>1,2,4</sup>. Genetic counselling is essential. However, routine screening for lung and liver AVMs, which is usually standard in HHT, is generally not indicated for CM-AVM unless clinical suspicion arises<sup>1,3</sup>. Cutaneous telangiectasias are benign but can be treated cosmetically, while arteriovenous malformations and fistulas may require embolisation, surgery, or radiosurgery.

#### **Declarations of Conflicts of Interest:**

None declared.

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