Multiple lentigines in *RASA1*-associated capillary malformation-arteriovenous malformation syndrome

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INTRODUCTION

Capillary malformation-arteriovenous malformation (CM-AVM) is the most common manifestation of *RASA1* mutation.[1] The clinical manifestations of CM-AVM syndrome are varied. The characteristic findings of the disease are capillary malformations with or without other fast-flow lesions (arteriovenous malformations [AVMs] and/or arteriovenous fistulas). However, pigmented lesions have not been reported in *RASA1* associated with CM-AVM syndrome. Here we report a case of multiple lentigines in a patient with *RASA1* mutation-associated CM-AVM syndrome.

CASE REPORT

A 59-year-old man presented with recurrent upper gastrointestinal (GI) bleeding leading to refractory iron-deficiency anemia. His father also died due to GI bleeding at the age of 63. Physical examination revealed multiple round to oval-shaped, well-demarcated, brown-to-black macules located on the lips, buccal mucosa, palms, and genitalia (Fig 1). The onset of these pigmentary lesions was unknown. Moreover, multiple small, reddish, pinpoint papules located on the tongue and lower labial mucosa were observed (Fig 1). He denied having any family members with the same cutaneous presentation. From the constellation of presenting signs, the diagnosis of PTEN-hamartoma tumor syndrome (Bannayan-Riley-Ruvalcalba syndrome [BRRS]) was suspected. The differential diagnoses included hereditary hemorrhagic telangiectasia, CM-AVM syndrome, Peutz-Jeghers syndrome, and Bandler syndrome. Esophagogastroduodenoscopy performed to find the cause of GI bleeding revealed AVM of the duodenum. Whole exome sequencing was chosen due to broad differential diagnosis, which revealed a heterozygous frameshift 1 basepair deletion in *RASA1* (NM_002890.2: c499delG [p.Glu167LysfsTer7]). The patient was treated with band ligation of duodenal AVM and iron supplement to correct iron-deficiency anemia. For the cutaneous lesions, pigment and vascular specific laser are options for cosmetic reasons. However, the patient did not undergo laser therapy, as they were not his concern.

Abbreviations used:

AVM:	arteriovenous malformation
BRRS:	Bannayan-Riley-Ruvalcalba syndrome
CM-AVM:	capillary malformation-arteriovenous malformation
GI:	gastrointestinal

DISCUSSION

Our patient represents an atypical presentation of *RASA1*-associated CM-AVM syndrome. The diagnosis was challenging, as GI hemorrhage and pigmentary lesions are uncommon in CM-AVM syndrome. The *RASA1* gene encodes for a p120-Ras GTPase-activating protein (p120-RasGAP), which is involved in many cellular signaling pathways, including the Ras/MAPK and PI3K pathways. Both pathways are important in the regulation of cellular

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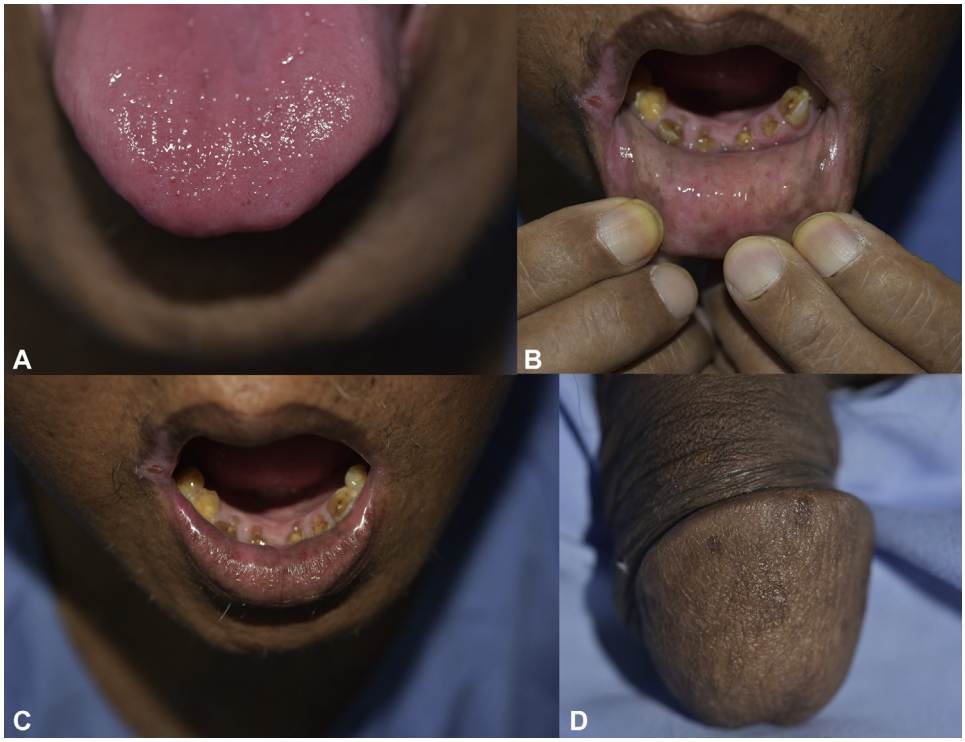

Fig 1. Multiple pinpoint reddish telangiectasia-like papules on the tongue and lower labial mucosa (**A, B**) with multiple lentigines on the lips and genitalia (**C, D**).

development (Fig 2).[2,3] Loss-of-function mutations in *RASA1* result in developmental abnormalities of the vascular structure.[1,4] To date, CM-AVM syndrome and Parkes Weber syndrome have been reported to be related to loss-of-function mutations of the *RASA1* gene.[1] CM-AVM syndrome is an autosomal dominant inherited disorder. However, de novo mutations can occur in around 25%-32%.[1,5,6] The clinical manifestations of CM-AVM syndrome exhibit both intrafamily and interfamily variations. These phenotypic variations are proposed to be the result of opportunities to obtain the second pathogenic variant.[7,8] Currently, there are 2 clinical phenotypes of CM-AVM syndrome, CM-AVM1 and CM-AVM2, which are caused by *RASA1* and *EPHB4* mutations, respectively.[9] Both CM-AVM phenotypes are characterized by typical CM lesions occurring early in life. Typical CM lesions are single to multiple, round to oval shape, pinkish to purplish-red or reddish-brown macules with a perilesional pale halo located on the skin and rarely on the mucous membranes.[5,10] Less frequently, pinpoint reddish telangiectasia-like papules as in our patients' presentation are also reported.[11] These telangiectasias are found mostly in CM-AVM2, resembling the clinical pictures of hereditary hemorrhagic telangiectasia.[9] Besides, the AVMs/arteriovenous fistulas in CM-AVM syndrome can be found in the central nervous system (brain and spine) and can cause neurologic defects.[1,8] GI hemorrhage is not a common presentation in *RASA1*-associated CM-AVM syndrome compared to hereditary hemorrhagic telangiectasia.

There are reports of a hyperpigmented light-brown network background of CM lesions demonstrated by dermoscopic examination.[5,12] It is still doubtful whether there is a combination of café-au-lait macules within the CM lesions.[12] However, to our knowledge, there have not been reports of isolated pigmentary lesions which have not occurred within the CM lesions in *RASA1*-associated CM-AVM syndrome. Our patient presented with multiple lentigines that resembled those in several inherited syndromes, such as familial lentiginosis syndrome (Peutz-Jeghers syndrome; Carney complex syndrome; Lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness syndrome; and BRRS) or acquired hyperpigmentation disorders (Laugier-Hunziker syndrome and Cronkhite-Canada syndrome). However, CM and/or AVM are not found in these diseases except for BRRS. The clinical characteristics of other systemic involvement, such as cardiac abnormalities and GI polyposis, can help in the differential diagnosis.[13] There is an interesting point in lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness syndrome

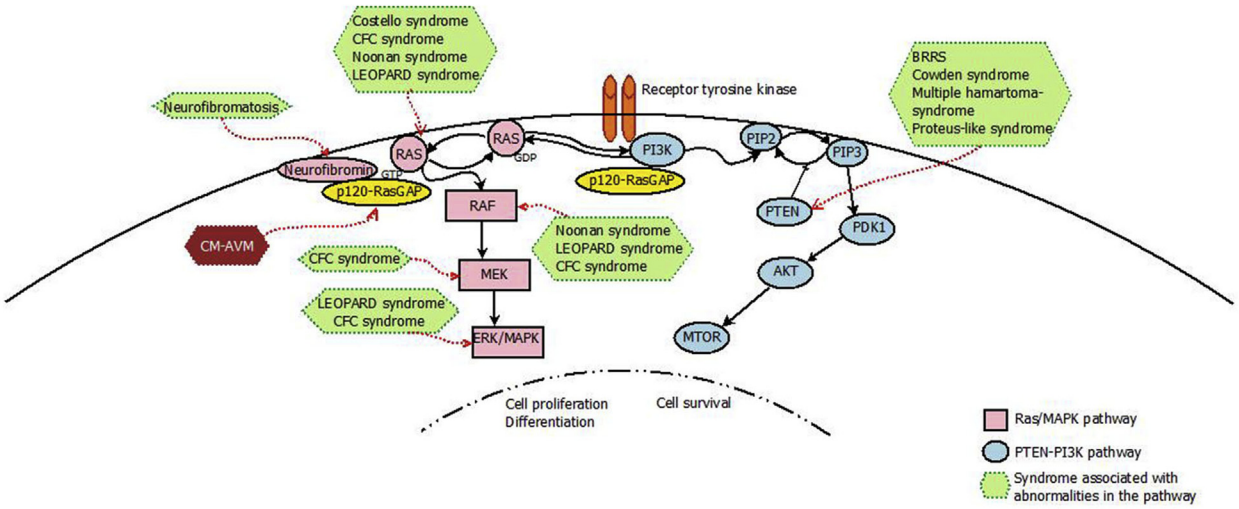

Fig 2. Schematic diagram representing the Ras/MAPK and PTEN-PI3K pathways as well as syndrome associated with abnormalities in these pathways.

(Noonan syndrome with multiple lentigines, formerly called LEOPARD syndrome) and BRRS, which are caused by genetic abnormalities involving the Ras and PTEN pathway, respectively, as p120-RasGAP is involved in part of their signaling transduction pathway.

The proposed pathogenesis of pigmentary lesions in our case may result from the abnormal Ras-associated signal transduction pathway, which is involved in melanocyte proliferation and survival, as demonstrated in Noonan syndrome with multiple lentigines or café-au-lait macules in neurofibromatosis type I.[13] Moreover, p120-RasGAP is involved in the PI3K signaling pathway, and there is crosstalk within the Ras/MAPK and PTEN-PI3K pathways. These may explain the phenotypic similarity of our case with BRRS (Fig 2).[2,3] Further investigation of this issue is suggested to explain the underlying pathogenesis of these presentations.

In summary, we report a case with recurrent GI hemorrhage and multiple lentigines, which is an atypical presentation of *RASA1*-associated CM-AVM syndrome. In patients who present with recurrent upper GI hemorrhage, the skin should be thoroughly examined. The characteristic cutaneous findings are helpful to narrow down the differential diagnosis. Lastly, genetic testing is essential for making the definite diagnosis.

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