Propranolol as a potentially novel treatment of arteriovenous malformations

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Key words: arteriovenous malformation; MAPK; propranolol.

INTRODUCTION

Arteriovenous malformations (AVMs) are characterized by a snarled tangle of arteries and veins that are connected to each other through a bypass in the capillary bed.[1,2] AVMs can occur anywhere on the body but are most commonly in the brain, lungs, pelvis, and extremities.[1,2] AVMs can be either asymptomatic or cause intense pain or bleeding and can lead to serious medical problems.[3,4] The diagnosis of an AVM involves a combination of vascular imaging studies, such as Doppler ultrasound, computerized axial tomography, magnetic resonance angiography, and histologic examination of tissue biopsies. The clinical management of an AVM ranges from conservative approaches for asymptomatic AVMs and AVMs with minor symptoms to percutaneous sclerotherapy, endovascular embolization, or surgery, which is often required for symptomatic AVMs.[3,4]

Propranolol is a nonselective blocker of the β-adrenergic receptor and has been used for treatment of proliferative infantile hemangiomas.[5] The vasoconstrictive and antiangiogenic effects of propranolol led us to explore its potential application for the treatment of AVMs. Herein, we report on a 19-year-old woman with a diagnosis of an AVM presenting with a large patch and right lower limb hypertrophy. The patient was treated with oral propranolol for 5 months, during which time regression of the patch and limb hypertrophy was observed. The activation profiles of the mitogen-activated protein kinase (MAPK) pathway were also investigated in the ectatic blood vessels. Our study showed that oral propranolol might be a potentially novel treatment option for AVMs, and the MAPK signaling pathway contributes to the progression of AVMs.

Abbreviations used:

AVM:	arteriovenous malformation
MAPK:	mitogen-activated protein kinases
p-AKT:	phosphorylated protein kinase B
p-ERK:	phosphorylated extracellular signal-regulated kinases
p-JNK:	phosphorylated c-Jun N-terminal protein kinases
p-PI3K:	phosphorylated phosphatidylinositol 3-kinases
p-S6K:	phosphorylated ribosomal s6 kinase

CASE

A 19-year-old female patient had a large erythematous patch and right lower limb hypertrophy. At birth, both the erythematous patch and the right lower limb hypertrophy were noted. The patch was initially pale red and flat with irregular borders, which measured 3×2 cm^2. By the time the patient visited our clinic, the patch appeared bright red and was associated with a protuberance which measured 8.8×6.6 cm^2 (Fig 1, *A*). Concurrently, the right lower limb hypertrophy had slowly grown progressively

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Funding sources: Supported by the National Institute of Health grants AR063766 (to Dr Tan) and AR47551 and AR59244 (to Dr Nelson), the American Society for Laser Medicine and Surgery research grants F03.12 and F01.13 (to Dr Tan), and the Natural Science Foundation of Hunan Province grant S2011J5043 (to Dr Lu).

Conflicts of interest: None declared.

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JAAD Case Reports 2018;4:355-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2017.11.005

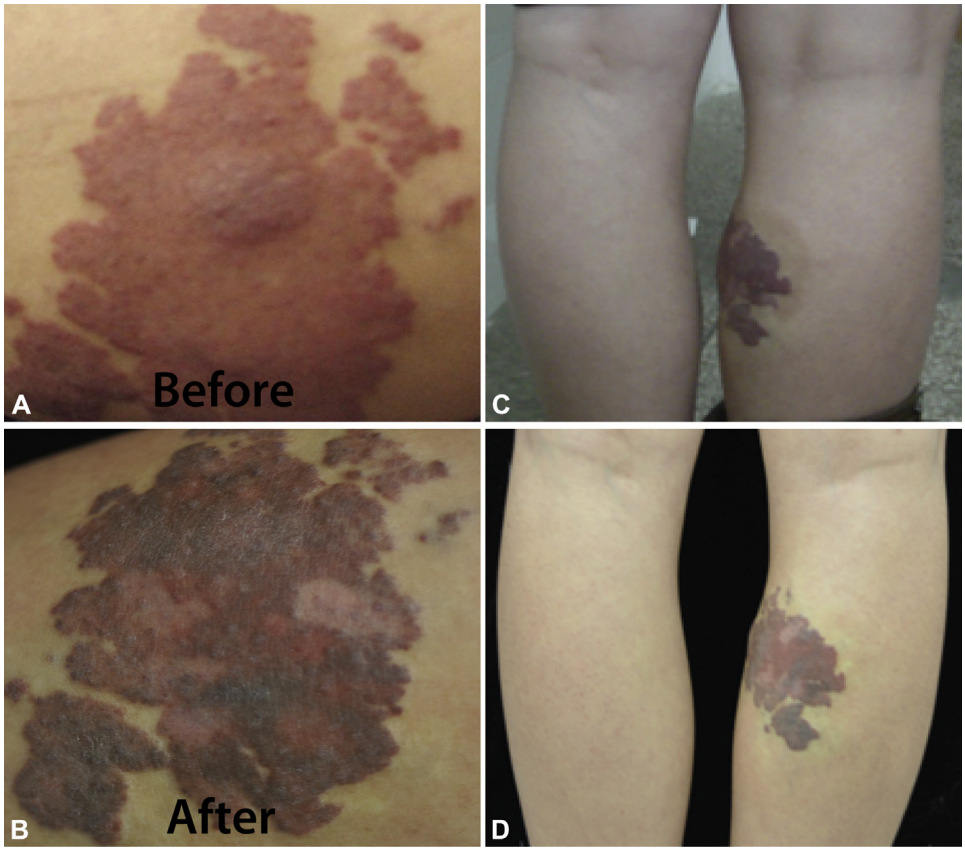

Fig 1. Patch and limb hypertrophy improved in the patient with an arteriovenous malformation treated with oral propranolol. The raised macular lesion as a protuberance before treatment (**A**), and lesion after 40 days of treatment (**B**). Regression of right lower limb hypertrophy after 40 days (**C**) and 5 months (**D**) of treatment.

larger over time. The patient had not received any treatment before her arrival at our clinic. Multiple tortuous, dilated, and tangled arteries and veins, mainly involving the inferior and superior lateral genicular arteries, tibial-fibular trunk, greater saphenous and popliteal veins, throughout the right lower limb were identified on a color-coded duplex ultrasound and helical computerized axial tomography scan with contrast. On the basis of the clinical presentation and imaging studies, a diagnosis of AVM was confirmed.

The risk factors and potential contraindications to using propranolol were fully discussed with the patient and her family before informed consent was sought and obtained. Subsequently, the patient was prescribed as the initial treatment oral propranolol 20 mg 3 times per day. During the first 40 days of propranolol treatment, the patch was noted to change from a bright red color to a dark purple. Moreover, the protuberance had flattened and smoothened out with the adjacent normal skin (Fig 1, *B* and *C*). A follow-up duplex ultrasound showed a significant decrease in blood flow through the AVMs. Thereafter, because the patient was complaining of dizziness and bradycardia, the propranolol dosage was reduced to 20 mg 2 times per day. After 5 months of oral propranolol treatment, full regression of the right lower limb hypertrophy was observed and became more similar to the normal left leg (Fig 1, *D*). Unfortunately, the patch and protuberance recurred after oral propranolol was discontinued, and the patient was subsequently referred to our plastic surgeon colleagues for resection of the arteriovenous nidus. After surgically removed, the AVM nidi were collected for the follow-up immunohistochemistry studies.

We next studied the activation profiles of several key kinases in the MAPK pathway to elucidate the potential pathologic mechanisms underlying the progression of AVM. Histopathologic examination of a deep tissue biopsy from the erythematous patch showed numerous proliferative ectatic blood vessels with thickened walls involving capillaries, arteries, and veins (Fig 2, *A-C*). Immunohistochemistry showed the blood vessels had strong immunoreactive signals for the phosphorylated c-Jun N-terminal

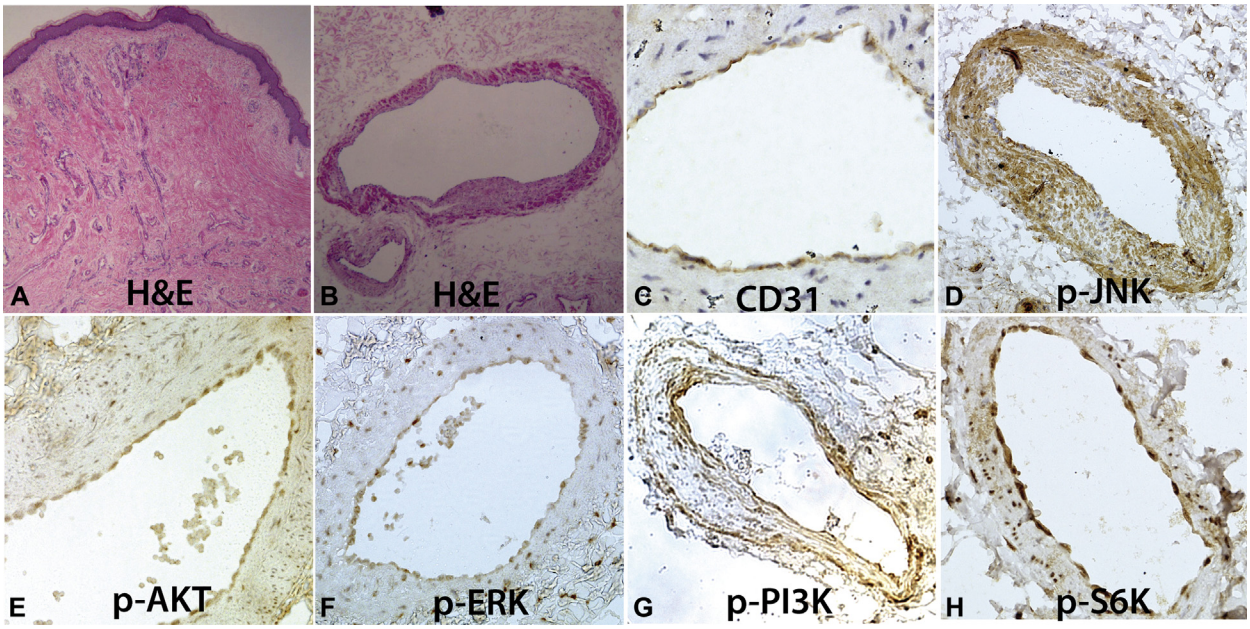

Fig 2. A-H, Histologic examination the patient's AVM. **A** and **B**, H&E staining. **C**, Immunostaining with CD31, an endothelial cell marker. **D-H**, Activation of various mitogen-activated protein kinases in AVM blood vessels. Immunostaining with p-JNK (**D**), p-AKT (**E**), p-ERK (**F**), p-PI3K (**G**), and p-S6K (**H**). *AVM*, Arteriovenous malformation; *H&E*, hematoxylin-eosin staining; *p-AKT*, phosphorylated protein kinase B; *p-ERK*, phosphorylated extracellular signal-regulated kinases; *p-JNK*, phosphorylated c-Jun N-terminal protein kinases; *p-PI3K*, phosphorylated phosphatidylinositol 3-kinases; *p-S6K*, phosphorylated ribosomal s6 kinase.

protein kinase (p-JNK) throughout the entire vessel wall, including the endothelial cells, smooth muscle cells, and surrounding fibroblasts (Fig 2, *D*). The phosphorylated ribosomal s6 kinase (p-S6K), extracellular signal-regulated kinases (p-ERK), protein kinase B (p-AKT), and phosphatidylinositol 3-kinases (p-PI3K) showed moderate-to-weak immunoreactive signals in the endothelial cells and pericytes (Fig 2, *E-H*).

DISCUSSION

The etiology of AVMs remains incompletely understood but angiogenesis has been speculated as one of the pivotal molecular mechanisms. Genetic defects in some angiogenic factors, such as the angiogenic factor with G patch and FHA domains 1 and RAS p21 protein activator, have been reported in AVMs.[6,7] However, it is unclear how these mutations lead to the specific vascular anomalies and limb hypertrophy observed in some AVMs. We recently determined that the MAPK pathway is consecutively activated in patients with capillary vascular malformations (eg, port wine stain).[8] We hypothesized that similar mechanisms might contribute to the progression of AVMs. Indeed, we found that various kinases involving the MAPK pathway were activated in this AVM, including JNK, which was strongly activated throughout the entire blood vessel wall. Activation of other kinases, such as AKT, EKR, S6K, and PI3K, were confined primarily to the endothelial cells. The aberrant activation of each kinase showed a cell-type specific pattern, suggesting distinct roles in the pathologic development of AVMs in different cell types.

In some patients, the high blood flow resulting from the extensive arteriovenous shunting through the limb's AVM is the major barrier to overcome before a successful treatment protocol can be developed.[9,10] In general, treatment options are surgical resection of the AVM nidus, endovascular intervention, or a combination thereof.[9,10] Several reports have documented the successful treatment of proliferative infantile hemangiomas with oral propranolol.[5] In our AVM case, oral propranolol induced significant remission of the patch and full regression of the right lower limb hypertrophy. Propranolol was well tolerated and reasonably safe over a treatment period of 5 months. However, the patch and protuberance recurred once propranolol was discontinued. The mechanism underlying this recurrence is unknown and will be the subject of future investigation. Our results suggest that propranolol might be a potentially novel treatment option for patients with AVM.

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