

Treatment of Infantile Hemangiomas in Concomitant Tuberous Sclerosis Complex Should Prompt Evaluation for Cardiac Rhabdomyomas Prior to Initiation of Propranolol

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PRACTICE POINTS

- Dermatologists may see patients with infantile hemangiomas (IHs) and tuberous sclerosis complex (TSC); therefore, they should be familiar with TSC diagnostic criteria to reach a prompt diagnosis and make appropriate referrals.
- Cardiac evaluation is not routinely required prior to systemic treatment of IH, but knowledge of cardiac findings in TSC should prompt cardiac clearance prior to β -blocker initiation.

To the Editor:

Cardiac rhabdomyomas are benign hamartomas that are common in patients with tuberous sclerosis complex (TSC).¹ We describe a patient who presented with large infantile hemangiomas (IHs) and hypopigmented macules, which prompted further testing that eventually showed concomitant multiple cardiac rhabdomyomas in the context of TSC.

A 5-week-old girl—who was born at 38 weeks and 3 days' gestation via uncomplicated vaginal delivery—was

referred to our pediatric dermatology clinic for evaluation of multiple erythematous lesions on the scalp and left buttock that were first noticed 2 weeks prior to presentation. There was a family history of seizures in the patient's mother. The patient's older brother did not have similar symptoms.

Physical examination revealed 2 nonulcerating erythematous nodules on the middle and posterior left vertex scalp that measured 2.5×2 cm (Figure 1A) as well as 1 bright red plaque on the left buttock (Figure 1B). Five hypopigmented macules, ranging from 5 mm to 1.5 cm in diameter, also were detected on the left thorax (Figure 2A) as well as the middle and lower back (Figure 2B). These findings, along with the history of seizures in the patient's mother, prompted further evaluation of the family history, which uncovered TSC in the patient's mother, maternal aunt, and maternal grandmother.

The large IHs on the scalp did not pose concerns for potential functional impairment but were still considered high risk for permanent alopecia based on clinical practice guidelines for the management of IH.² Treatment with oral propranolol was recommended; however, because of a strong suspicion of TSC due to the presence of 5 hypopigmented macules

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Drs. Buethe, Uwakwe, and Glick report no conflict of interest. Dr. Di Franco has served as a consultant for Novo Nordisk and is an advisory board member for Scharper and Servier.

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measuring more than 5 mm in diameter (≥ 3 hypopigmented macules of ≥ 5 mm is one of the major criterion for TSC), the patient was referred to cardiology prior to initiation of propranolol.

Echocardiography revealed 3 intracardiac masses measuring 4 to 5 mm in diameter in the left ventricle (LV), along the interventricular septum and the LV posterior wall. These masses were consistent with rhabdomyomas (Figure 3)—a major criterion for TSC—which had not been detected by prenatal ultrasonography. No obstruction to LV inflow or outflow was observed. Additionally, no arrhythmias were detected on electrocardiography.

The patient was cleared for propranolol, which was slowly uptitrated to 2 mg/kg/d. She completed the course without adverse effects. The treatment of IH was successful with substantial reduction in size over the following months until clearance. She also was referred to neurology for magnetic resonance imaging of the brain, which showed a 3-mm subependymal nodule in the lateral right ventricle, another major feature of TSC.

Cardiac rhabdomyomas are benign hamartomas that affect as many as 80% of patients with TSC¹ and are

primarily localized in the ventricles. Although cardiac rhabdomyomas usually regress over time, they can compromise ventricular function or valvular function, or both, and result in outflow obstruction, arrhythmias, and Wolff-Parkinson-White syndrome.³ Surgical resection may be needed in patients whose condition is refractory to medical management for heart failure.

The pathophysiologic mechanism behind the natural involution of cardiac rhabdomyomas has not been fully elucidated. It has been hypothesized that these masses stem from the inability of rhabdomyoma cells to divide after birth due to their embryonic myocyte derivation.⁴

According to the TSC diagnostic criteria from the Tuberous Sclerosis Complex International Consensus Group, at least 2 major features or 1 major and 2 minor features are required to make a definitive diagnosis of TSC. Cutaneous signs represent more than one-third of major features of TSC; almost all patients with TSC have skin findings.⁵

Identification of pathogenic mutations in either *TSC1* (on chromosome 9q34.3, encoding for hamartin) or *TSC2* (on chromosome 16p13.3, encoding for tuberlin), resulting in constitutive activation of mammalian target of rapamycin and subsequent increased cell growth, is sufficient for a definitive diagnosis of TSC. However, mutations cannot be identified by conventional genetic testing in as many

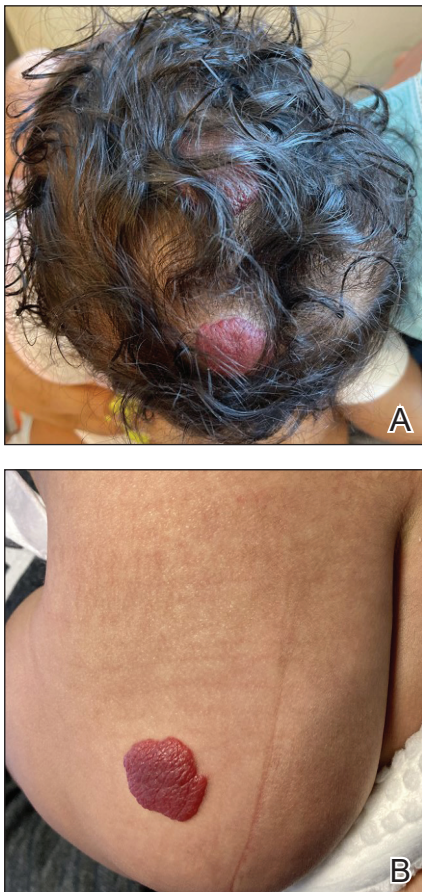


FIGURE 1. Infantile hemangiomas. A, Two 2.5×2-cm erythematous nodules on the middle and posterior left vertex scalp. B, A bright red plaque on the left buttock.

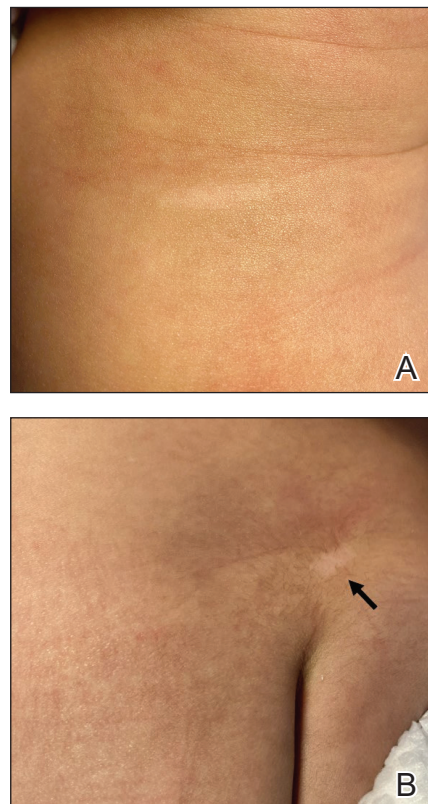


FIGURE 2. A and B, Hypopigmented macules on the left thorax and lower back.

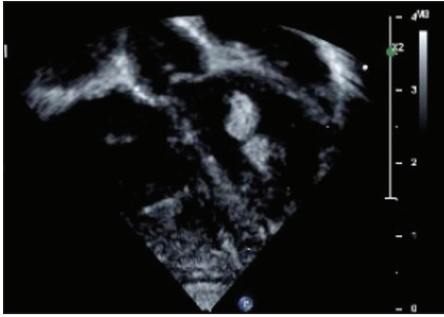


FIGURE 3. Echocardiography showed 2 (of 3 total) 4- to 5-mm intracardiac masses in the left ventricle, along the interventricular septum and posterior wall, consistent with rhabdomyomas.

as one-quarter of patients with TSC; therefore, a negative result does not exclude TSC if the patient meets clinical diagnostic criteria.

Although a cardiology workup is indicated prior to initiating propranolol in the presence of possible cardiac rhabdomyomas, most of those lesions are hemodynamically stable and do not require treatment. There also is no contraindication for β -blocker therapy. In fact, propranolol has been reported as a successful treatment in rhabdomyoma-associated arrhythmias in children.⁶ Notably, obstructive cardiac rhabdomyomas have been successfully treated with mammalian target of rapamycin inhibitors, such as sirolimus⁷ and everolimus.⁸

Baseline cardiology screening with echocardiography prior to initiating propranolol for treatment of IH is not routinely indicated in babies with uncomplicated IH. However, in a patient with TSC, cardiology screening is necessary to rule out rhabdomyomas with associated arrhythmias or obstructed blood flow, or both, prior to initiating treatment.

We presented a case of concomitant IH and TSC in a patient with cardiac rhabdomyomas. The manifestation of large IHs in our patient prompted further testing that revealed multiple cardiac rhabdomyomas in the context of TSC. It is imperative for cardiologists, cardiac surgeons, and dermatologists to be familiar with the TSC diagnostic criteria so that they can reach a prompt diagnosis and make appropriate referrals for further evaluation of cardiac, neurologic, and ophthalmologic signs.

REFERENCES

1. Frudit P, Vitturi BK, Navarro FC, et al. Multiple cardiac rhabdomyomas in tuberous sclerosis complex: case report and review of the literature. *Autops Case Rep.* 2019;9:e2019125. doi:10.4322/acr.2019.125
2. Krowchuk DP, Frieden IJ, Mancini AJ, et al; Subcommittee on the Management of Infantile Hemangiomas. Clinical practice guideline for the management of infantile hemangiomas. *Pediatrics.* 2019;143:e20183475. doi:10.1542/peds.2018-3475
3. Venugopalan P, Babu JS, Al-Bulushi A. Right atrial rhabdomyoma acting as the substrate for Wolff-Parkinson-White syndrome in a 3-month-old infant. *Acta Cardiol.* 2005;60:543-545. doi:10.2143/AC.60.5.2004977
4. DiMario FJ Jr, Diana D, Leopold H, et al. Evolution of cardiac rhabdomyoma in tuberous sclerosis complex. *Clin Pediatr (Phila).* 1996;35:615-619. doi:10.1177/000992289603501202
5. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49:243-254. doi:10.1016/j.pediatrneurol.2013.08.001
6. Kathare PA, Muthuswamy KS, Sadasivan J, et al. Incessant ventricular tachycardia due to multiple cardiac rhabdomyomas in an infant with tuberous sclerosis. *Indian Heart J.* 2013;65:111-113. doi:10.1016/j.ihj.2012.12.003
7. Breathnach C, Pears J, Franklin O, et al. Rapid regression of left ventricular outflow tract rhabdomyoma after sirolimus therapy. *Pediatrics.* 2014;134:e1199-e1202. doi:10.1542/peds.2013-3293
8. Chang J-S, Chiou P-Y, Yao S-H, et al. Regression of neonatal cardiac rhabdomyoma in two months through low-dose everolimus therapy: a report of three cases. *Pediatr Cardiol.* 2017;38:1478-1484. doi:10.1007/s00246-017-1688-4