LETTERS TO THE EDITOR WILEY

Multiple hypomelanotic macules in an infant cannot be ignored

To the editor:

A 9-month-old girl presented with multiple hypomelanotic macules that had been present since birth. Previously, she had been diagnosed with nevus depigmentosus and treated with intermittent topical emollient and sun protective measures; however, she exhibited no improvement. One week prior to presentation in our clinic, the patient's mother had observed a shagreen patch on the patient's back, as well as more than 10 new hypomelanotic macules on her trunk and extremities. The parents recalled no history of infantile spasms or seizures.

Physical examination revealed multiple depigmented or hypopigmented polygonal or guttate macules, measuring 0.2 to 2.0 cm in diameter, over the patient's trunk and limbs (Figure 1A). No fluorescence reaction was observed under Wood's lamp examination. A shagreen patch with a pigskin-like surface was found on the patient's torso (Figure 1B, black arrow). The patient's mother also noted the presence of similar lesions on the patient's trunk and lumbosacral area (Figure 2A); multiple dome-shaped, pink-tan papules (facial angiofibromas) on her cheeks (Figure 2B); and ash leaf macules on her neck (Figure 2C, red arrow). However, the patient's mother could not remember when those symptoms had initially occurred, so their duration could not be determined.

Echocardiography revealed multiple irregular abnormal echoes in the left and right ventricle and right ventricular outflow tract (Figure 1C), which had previously been detected on prenatal ultrasound at 24 weeks' gestation; subsequently, they had not been further investigated. After getting ethical approval from the Beijing Children's Hospital, next-generation sequencing was performed by

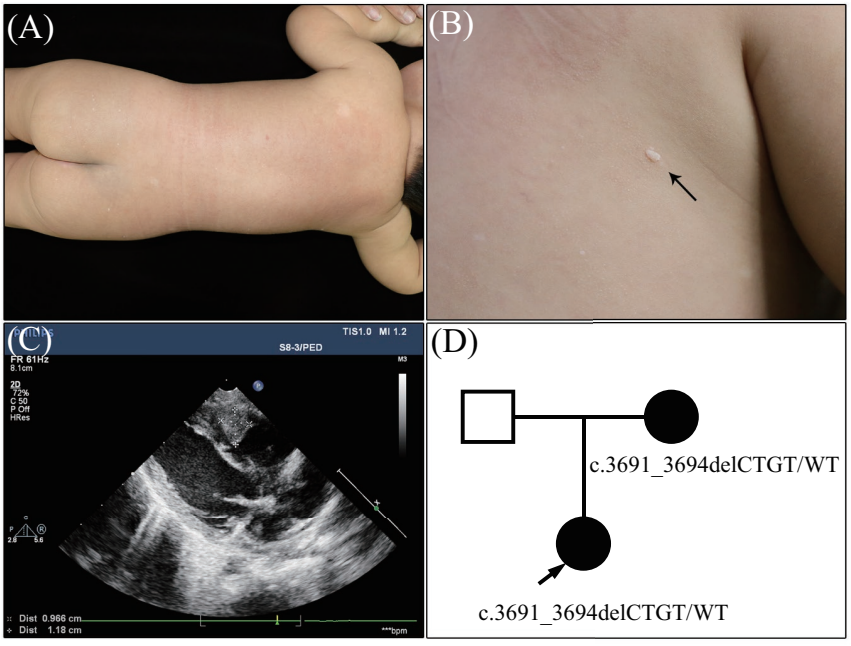

FIGURE 1 Skin lesion, echocardiography, and genetic examinations of the 9-month-old patient with tuberous sclerosis complex. (A) Hypopigmented macules over the trunk. (B) Shagreen patch (black arrow) on the torso. (C) Echocardiography revealed multiple irregular abnormal echoes in the right ventricle. (D) Pedigree of the patient.

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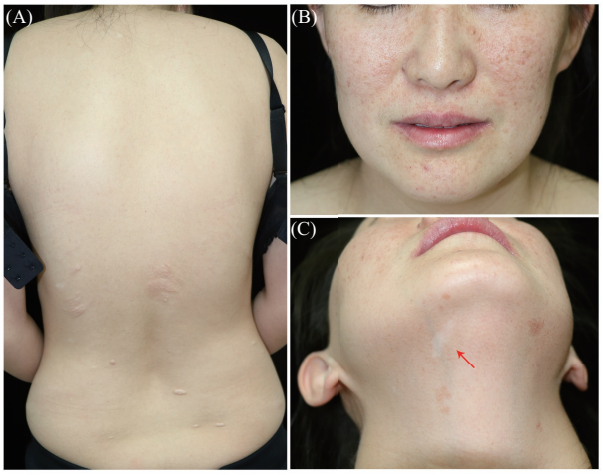

FIGURE 2 Skin lesion examination of the patient's mother showing (A) shagreen patch over the trunk, (B) facial angiofibromas on the cheeks, and (C) ash leaf macules (red arrow) on the neck.

using the patient's peripheral blood and Sanger sequencing was performed by using her parents' blood. The results revealed a known heterozygous frameshift mutation (c.3691_3694delCTGT, p.S1232Tfs*92) in *TSC2* in both the patient and her mother (Figure 1D).[1] Mutations in the *TSC1* and *TSC2* genes have been attributed to tuberous sclerosis complex (TSC). Therefore, a diagnosis of TSC was made in this family, based on the clinical and genetic findings.

TSC is an autosomal dominant neurocutaneous congenital disorder of cellular differentiation and proliferation that affects multiple organ systems including the skin, brain, kidneys, and heart; it also involves hamartoma formation.[2] Major cutaneous features in patients with TSC include hypomelanotic macules, typically the only cutaneous finding at birth; shagreen patch and facial angiofibromas, first observed at the ages of 2–8 years; and periungual fibromas, which develop later in childhood (after 4 years of age) and continue to form throughout adulthood. Because most major TSC criteria comprise cutaneous features in childhood, especially in a neonate, a thorough dermatologic examination frequently helps to establish the diagnosis.[3] Hypomelanotic macules or patches are the earliest sign of TSC and are present from birth in up to 90% of pediatric patients; three or more of these macules or patches (≥5 mm in diameter) are regarded as a major criterion for diagnosis. Hypomelanotic macules of TSC should be distinguished from nevus depigmentosus, nevus anemicus, post-inflammatory hypopigmentation, tinea versicolor, and vitiligo. Shagreen patch, a type of collagenoma, is another characteristic feature of TSC that very rarely appears before 1 year of age.[4] Because seizures and cardiac rhabdomyomas occur in the majority of affected infants, systemic examinations for asymptomatic infants with skin lesions alone should be performed. Notably, our patient presented with hypopigmented macules and shagreen patch; it was highly unusual for a neonate of this age with TSC to exhibit a complete spectrum of cutaneous presentations. Our patient received regular echocardiography follow-up; spontaneous resolution of cardiac rhabdomyomas was observed 2 years later.

Bin Zhang[1] , Xin Zhang[2], Huan Xing[1], Lin Ma[1]
[1]Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Heart Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Lin Ma, Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China
Email: bch_maleen@aliyun.com

CONSENT FOR PUBLICATION

Consent was obtained from the patient's parents.

CONFLICT OF INTEREST

None.

REFERENCES

1. Hung CC, Su YN, Chien SC, Liou HH, Chen CC, Chen PC, et al. Molecular and clinical analyses of 84 patients with tuberous sclerosis complex. BMC Med Genet. 2006;7:72.
2. Staley BA, Vail EA, Thiele EA. Tuberous sclerosis complex: Diagnostic challenges, presenting symptoms, and commonly Missed Signs. Pediatrics. 2011;127:e117-e125.
3. Hinton RB, Prakash A, Romp RL, Krueger DA, Knilans TK, International Tuberous Sclerosis Consensus Group. Cardiovascular manifestations of tuberous sclerosis complex and summary of the revised diagnostic criteria and surveillance and management recommendations from the International Tuberous Sclerosis Consensus Group. J Am Heart Assoc. 2014;3:e001493.
4. Bongiorno MA, Nathan N, Oyerinde O, Wang JA, Lee CR, Brown GT, et al. Clinical characteristics of connective tissue nevi in tuberous sclerosis complex with special emphasis on shagreen patches. JAMA Dermatol. 2017;153:660-665.

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