Tuberous Sclerosis With Segmental Overgrowth

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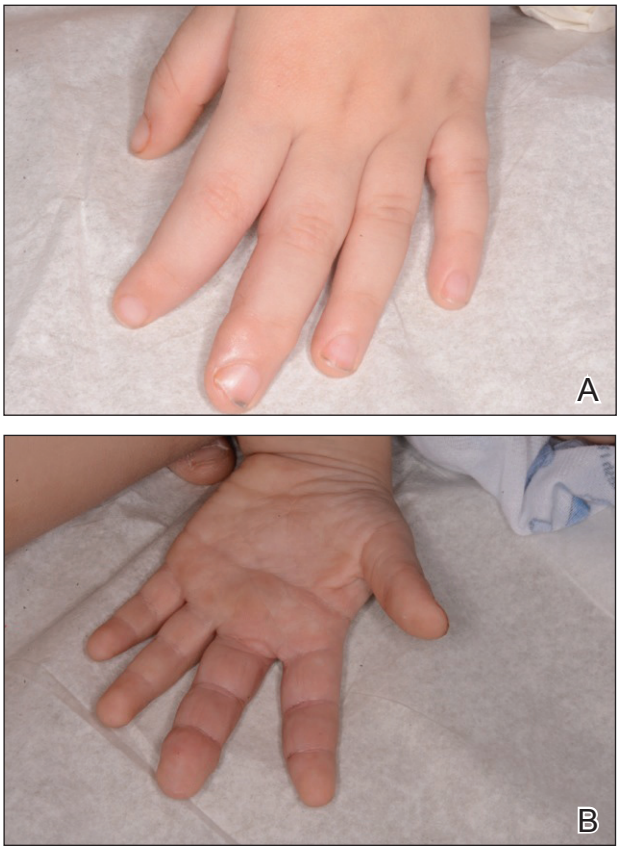
PRACTICE **POINTS**

- Tuberous sclerosis and Proteus syndrome share a common downstream effector pathway.
- For a patient to demonstrate features of both tuberous sclerosis and Proteus syndrome, he/she must have both a germline mutation (for tuberous sclerosis) as well as a postzygotic mutation (for Proteus syndrome) of this shared pathway.

To the Editor:

A 3-year-old boy with a history of tuberous sclerosis presented to our clinic for evaluation of bumps on the second and third fingers of the left hand. Physical examination revealed firm rubbery nodules on the palmar third metacarpophalangeal joint extending to the palm and the lateral aspect of the distal third dorsal finger. There also was asymmetric overgrowth of the left second and third digits consistent with bony segmental overgrowth (Figure).

Tuberous sclerosis and overgrowth syndromes including Proteus syndrome have mutations that share a common pathway, namely the PI3K/AKT/mTOR (phosphoinositide 3-kinase/alpha serine/threonine-protein kinase/mammalian target of rapamycin) pathway.[1] The mutations in tuberous sclerosis involve the loss of *TSC1* (TSC complex subunit 1) on chromosome 9 or *TSC2* (TSC complex subunit 2) on chromosome 16.[2] The protein products of these genes, hamartin and tuberin, act together as a tumor suppressor complex.[3] The inheritance pattern of tuberous sclerosis is autosomal dominant, though two-thirds of cases are due to de novo germline mutations.[4] The second copy of the gene must be lost spontaneously in any particular cell for the deleterious effects of the disease to manifest. The mutation in overgrowth syndromes including Proteus syndrome involves the activation of *AKT1* (AKT serine/threonine kinase 1) on chromosome 14. This mutation occurs in somatic cells as opposed to germ cells, as in tuberous



A and B, Enlarged second and third digits on the dorsal and palmar aspects of the left hand.

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sclerosis. This difference accounts for the mosaic expression of segmental overgrowth syndromes. This concept has been demonstrated in overgrowth syndromes such as Proteus syndrome, with cells from unaffected areas having different genetic makeup than those from affected tissues.[5] These mutations, though different, result in the downstream effects of unchecked messenger RNA translation and dysregulated cellular growth.

In our patient, we hypothesized that a small proportion of his postfertilization somatic cells underwent a second de novo mutation in the *AKT1* pathway, resulting in the bony overgrowth seen on the left hand. We suspected that this second mutation could be an activation of *AKT1*, the mutation seen in Proteus syndrome. Sequencing of the tissue may be performed in the future, especially if segmental overgrowth continues and necessitates therapy.

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