Recurrent Cerebriform Connective Tissue Nevus on the Foot of a Patient With Proteus Syndrome

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PRACTICE **POINTS**

- Proteus syndrome (PS) is a rare mosaic condition characterized by progressive overgrowth of skin, connective tissue, brain tissue, and other tissues.
- A somatic activating mutation of the *AKT1* gene has been identified as a cause for developing PS.
- Distinct cutaneous features, including cerebriform connective tissue nevi (CCTN), epidermal nevi, vascular malformations, and adipose abnormalities, can alert the dermatologist to the underlying condition before the onset of asymmetric skeletal overgrowth.
- The CCTN in PS grows throughout childhood but tends to remain stable in adulthood. Postponing surgical treatment until skin lesions stabilize appears to be the best option. However, for practical purposes, surgical intervention may be required at an earlier phase to address the severe functional and cosmetic consequences.

To the Editor:

A 12-year-old girl presented with discomfort and walking limitation caused by cutaneous masses on the plantar aspects of the feet with associated bone abnormalities that had started as several flesh-colored papules on the plantar surface of both feet at the age of 1 year. Over time the lesions gradually enlarged and formed irregular masses, more prominently on the right foot. At the age of 6 years, surgical correction was performed due to increased walking impairment and a skin examination that suggested connective tissue nevus. The results were good. However, the local tissue overgrowth recurred after 1 year. Slowly growing lesions were found at the surgical site, which necessitated hospitalization. Her medical history was negative for other disease. There was no family history of similar skin conditions and her parents were nonconsanguineous.

Physical examination revealed malnutrition and poor development in height as well as difficulty walking. She also had moderate scoliosis with a curve to the left. Dermatological examination showed multiple reddish cerebriform hyperplasia in both plantar areas; the right side was more severely involved (Figure 1A). There was macrodactyly of 2 toes on the right foot (Figure 1B). All results of routine blood examinations were within reference range. There were no abnormalities noted in the abdominal ultrasound and cardiac examinations. Plain radiographs of the spine and feet demonstrated scoliosis and exostosis on the calcaneus and bottom of the scaphoid. Histopathologic examination of tissue from the plantar cerebriform hyperplasia revealed hyperkeratosis, slight acanthosis

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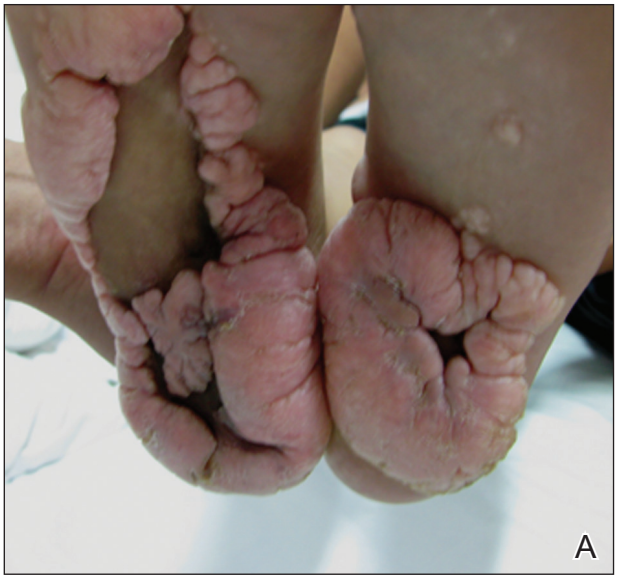

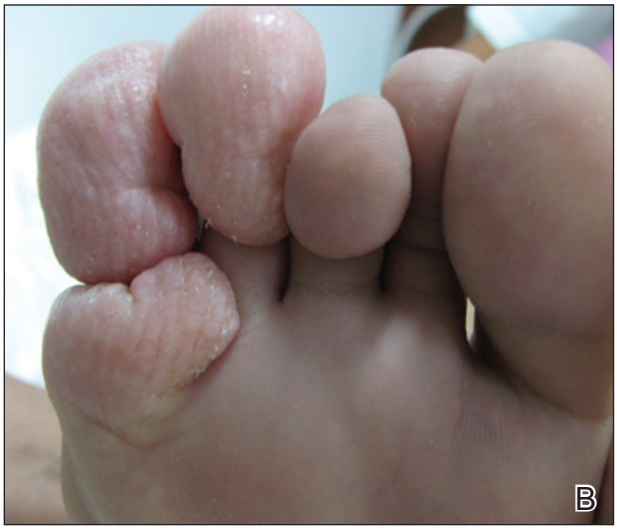

Figure 1. Multiple reddish plantar cerebriform hyperplasia before the second surgery (A) and macrodactyly of 2 toes on the right foot (B).

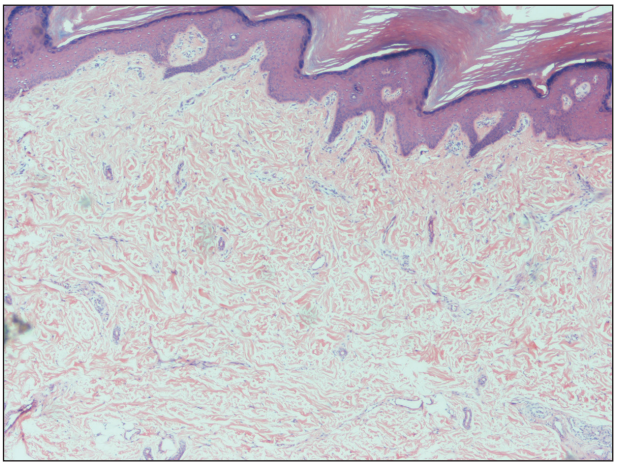

Figure 2. Hyperkeratosis, slight acanthosis and papillomatosis in the epidermis, and dense collagen bands in the dermis (H&E, original magnification ×200).

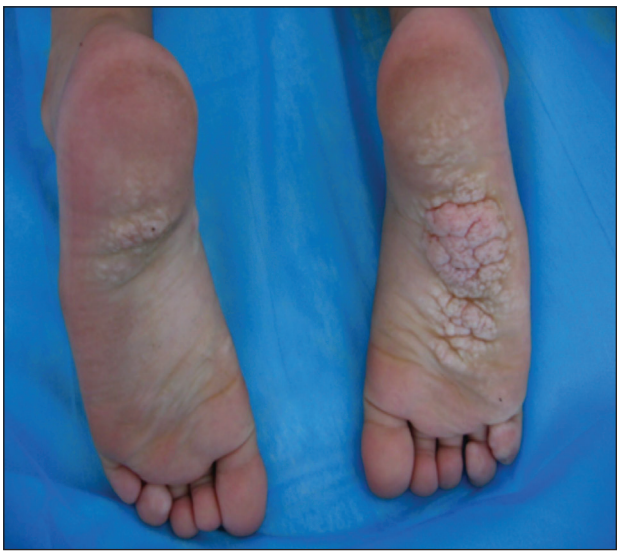

Figure 3. The skin graft area was healed 1 year following surgery.

and papillomatosis in the epidermis, and dense collagen bands and sparse elastic fibers in the dermis (Figure 2).

Given the clinical and radiologic manifestation, the diagnosis of Proteus syndrome (PS) was established. After taking into account the severe discomfort and the success of the first surgery, we performed a resection and full-thickness skin graft surgery once again. The feet recovered without any discomfort in daily life. The appearance of the skin graft area was normal 1 year following surgery (Figure 3). She was treated with spinal plate fixation at another institution, progressed well for 2 years, and was subsequently lost to follow-up.

Proteus syndrome is a multisystem disorder with a difficult diagnosis due to the variability of its manifestations. The worldwide incidence of this rare disorder is less than 1 per 1 million individuals, and it is thought to be caused by a somatic genetic alteration.[1] Clinical characteristics include bone abnormalities, vascular malformations, dysregulation of fatty tissue, linear verrucous epidermal nevus, and cerebriform connective tissue nevus (CCTN). Although CCTN is not a common finding in patients with PS, it is considered a fairly specific sign with the greatest impact for the diagnosis of PS.[2]

The general feature of PS—asymmetric disproportionate overgrowth of tissues—appears at 6 to

18 months of age, which makes it challenging to diagnose disease earlier. The CCTN in our patient was present since 1 year of age.

To make a diagnosis of PS, one must have all the general criteria and various specific criteria. The revised diagnostic criteria for PS are given in the Table.[3] According to the diagnostic criteria, our patient fulfilled the mandatory general criteria and had plantar CCTN, epidermal nevus, and dysregulated adipose tissue. The CCTN has notable diagnostic value in mildly affected patients, as it is absent in diseases included in the differential diagnosis such as neurofibromatosis, Klippel-Trenaunay-Weber syndrome, Maffucci syndrome, and Bannayan-Riley-Ruvalcaba syndrome. Hemihyperplasia-multiple lipomatosis syndrome and CLOVES (congenital, lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/spinal/skeletal anomalies) syndrome also can present on the plantar surfaces, and lesions may be overgrown at birth but are softer and compressible, have wrinkles instead of deep folds, and tend to grow with the child rather than disproportionately as in PS.[4]

The epidermal nevi and vascular malformations generally do not spread or increase in number. In contrast, CCTN in PS grows throughout childhood but tends to remain stable in adulthood.[4] Postponing surgical treatment until skin lesions stabilize appears to be the best option. However, for practical purposes, surgical intervention may be required at an earlier phase to address the severe functional and cosmetic consequences. Some patients require multiple orthopedic procedures over the ensuing years or decades to control the hyperplasia.[3] New CCTN that developed from the prior surgical incision, macrodactyly of the fourth and fifth right toes, and scoliosis appeared when the patient came to our clinic for retreatment 1 year after the initial presentation. The asymmetrical and disproportionate overgrowth of tissues had moderately accelerated in that period. Considering the increasingly impaired walking, we performed a second surgery. On follow-up visits, the patient expressed improvement in daily life.

Studies had been performed to clarify the genetic bases of PS, and the somatic activating mutation in *AKT1* (AKT serine/threonine kinase 1) was reported to be the cause of the disease.[5,6] Germline *PTEN* (phosphatase and tensin homolog) mutations have been identified in some patients with overgrowth abnormalities of PS. However, given the misdiagnosis of PS with *PTEN* mutations and the notion that a gene alone cannot result in PS, the loss-of-function mutations of *LEMD3* that have been reported in familial cutaneous collagenomas also may be related to the abnormal growth of connective and bone tissues that are typical of PS.[7,8] Lindhurst et al[5] concluded that PS is caused by a somatic activating mutation in *AKT1*, which proved the hypothesis of somatic mosaicism and implicated activation of the PI3K-AKT pathway in the characteristic clinical

Diagnostic Criteria of Proteus Syndrome

General criteria (all of the following):

Mosaic distribution of lesions
Sporadic occurrence
Progressive course

Specific criteria categories[a]:

A. 1. Cerebriform connective tissue nevus
B. 1. Linear epidermal nevus
   2. Asymmetric, disproportionate overgrowth (one or more):
      (a) Limbs
      (b) Hyperostosis of the skull
      (c) Hyperostosis of the external auditory canal
      (d) Megaspondylodysplasia
      (e) Viscera: spleen/thymus
   3. Specific tumors before 2nd decade (one of the following):
      (a) Bilateral ovarian cystadenomas
      (b) Parotid monomorphic adenoma
C. 1. Dysregulated adipose tissue (either one):
      (a) Lipomas
      (b) Regional lipohypoplasia
   2. Vascular malformations (one or more):
      (a) Capillary malformation
      (b) Venous malformation
      (c) Lymphatic malformation
   3. Lung cysts
   4. Facial phenotype (all):
      (a) Dolichocephaly
      (b) Long face
      (c) Down slanting of palpebral fissures and/or minor ptosis
      (d) Low nasal bridge
      (e) Wide or anteverted nares
      (f) Open mouth at rest

[a]Either 1 from category A, 2 from category B, or 3 from category C.

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findings of overgrowth and tumor susceptibility in this disorder. *AKT1* is activated by loss-of-function mutations in *PTEN*, which explains why patients with these mutations (eg, those with the segmental overgrowth, lipomatosis, arteriovenous malformation, epidermal nevus, SOLAMEN [segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus] syndrome) and patients with activating mutations in *AKT1* (eg, those with PS) have overlapping but distinct clinical manifestations. Molecular genetic testing may be useful to confirm the diagnosis in individuals who meet clinical criteria and to establish the diagnosis in individuals with clinical findings that are ambiguous or mild. Further studies are necessary to progress the understanding and management of PS, which will require cooperation of geneticists, surgeons, and other specialists.

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