Proteus Syndrome: 2 Case Reports and a Review of the Literature

CDR Elizabeth Satter, MC, USN

GOAL

To understand Proteus syndrome to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Identify diagnostic criteria for Proteus syndrome.
2. Discuss the differential diagnosis of Proteus syndrome.
3. Describe treatment options for Proteus syndrome.

CME Test on page 296.

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Proteus syndrome is a rare condition that has a variable clinical presentation. The syndrome is characterized by asymmetric disproportionate enlargement of the limbs, skull, or vertebrae, associated with a number of cutaneous lesions. Herein, the clinical findings of 2 patients with Proteus syndrome are presented and the current clinical diagnostic criteria are reviewed.

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Dr. Satter is Head of Dermatopathology and Staff Dermatologist, Dermatology Department, Naval Medical Center, San Diego, California.

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Proteus syndrome is characterized by asymmetric disproportionate enlargement of the limbs, skull, or vertebrae, associated with a number of cutaneous lesions. The variability in clinical presentation often results in misdiagnosis, and currently no diagnostic test exists. Although not seen in every patient, cerebriform connective tissue nevi, most commonly located on the plantar foot, are almost pathognomonic for the condition. While on a US Navy humanitarian mission in Southeast Asia, 2 patients with Proteus syndrome were identified. Herein, the clinical findings of 2 patients are presented and the current clinical diagnostic criteria are reviewed.

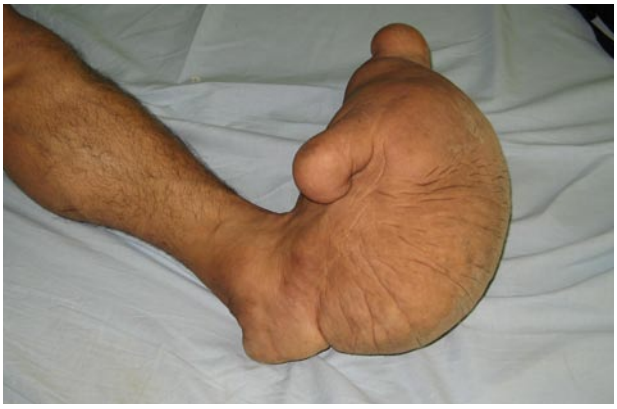

Figure 1. Asymmetric disproportionate overgrowth of left foot with a cerebriform connective tissue nevus on the plantar surface.

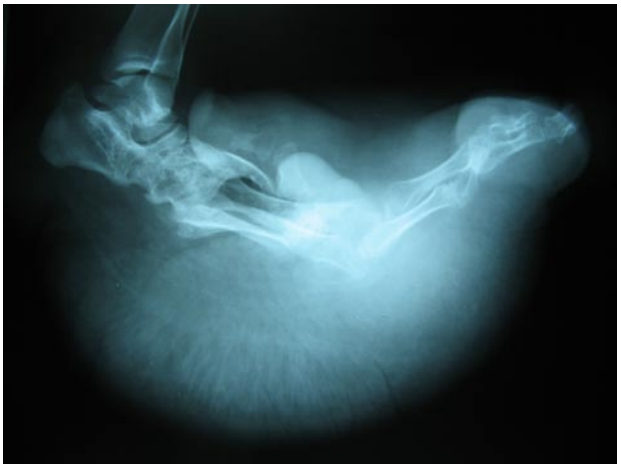

Figure 2. Enlargement of bones and soft tissues.

Case Reports

Patient 1—A 19-year-old man from Nias Island, Indonesia, presented for evaluation of a progressively enlarging left foot. The patient's father noted that his son had a small vascular lesion on his left calf at birth, but the father was unaware of a discrepancy in foot size until his son was a year old. Over the years, the vascular malformation increased proportionately to the son's growth; the foot, however, enlarged in a disproportionate fashion. At approximately 7 years of age, the plantar foot began to progressively thicken, resulting in pain and difficulty walking.

On examination, the patient had a substantially enlarged and distorted left foot with a large cerebriform connective tissue nevus on the plantar foot (Figure 1). A plain lateral radiograph of the foot confirmed enlargement of the bones and soft tissues (Figure 2). In addition, the patient's left calf was larger than the right calf and had an underlying vascular malformation (Figure 3). The patient did not have any café au lait spots, port-wine stains, varicosities, lipomas, or epidermal nevi. It was not possible to obtain a computed tomographic scan or magnetic resonance image to evaluate if there was involvement of other organ systems.

Patient 2—A 10-year-old boy presented for evaluation of a vascular lesion on his right chest. His mother noted that the lesion was present at birth and gradually had increased in size. On examination, the patient had asymmetric enlargement of his right chest associated with a poorly delineated vascular malformation that extended from his right chest and involved his upper abdomen and flank (Figure 4). The lower aspect of the lesion consisted of verrucous papules that intermittently bled and/or drained serosanguineous fluid. In addition, the patient had substantial cervical scoliosis and multiple large lipomas on his back and flank (Figure 5). No epidermal or connective tissue nevi were identified.

Comment

In 1979, Cohen and Hayden[1] described 2 patients with overgrowth of multiple tissues, connective tissue nevi, epidermal nevi, and hyperostoses. Subsequently, Wiedemann et al[2] named the condition Proteus syndrome after the Greek god Proteus to denote its polymorphous clinical presentation. Awareness of the syndrome was heightened when Joseph Merrick, known as "The Elephant Man," was diagnosed with

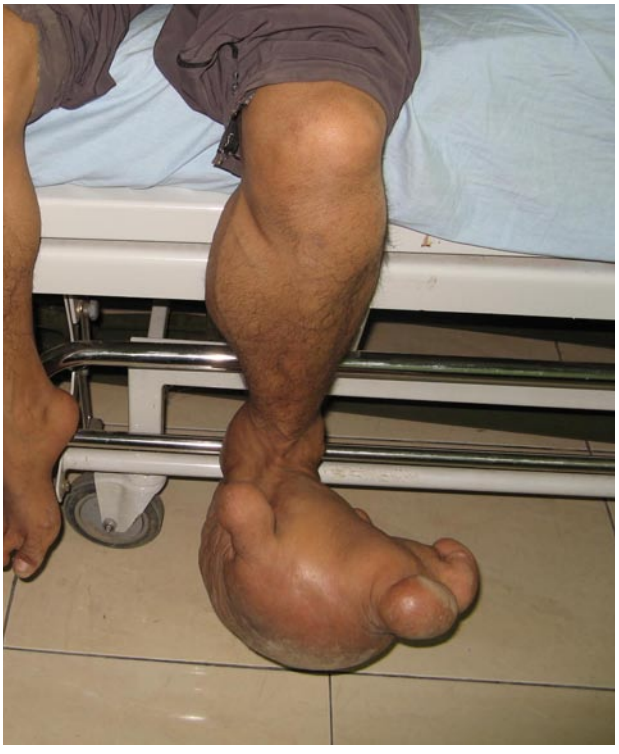

Figure 3. Enlargement of left calf with an underlying vascular malformation.

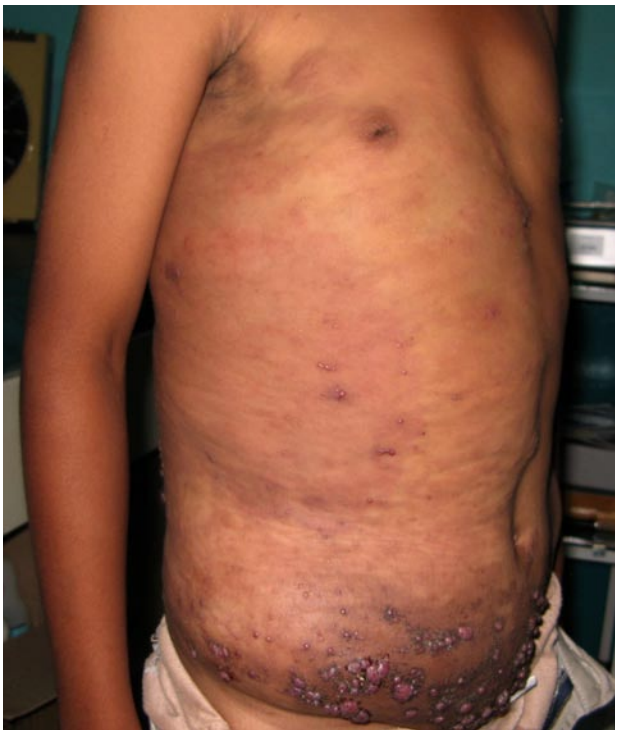

Figure 4. Poorly delineated vascular malformation involving the chest, abdomen, and flank, with verrucous papules at the lower aspect.

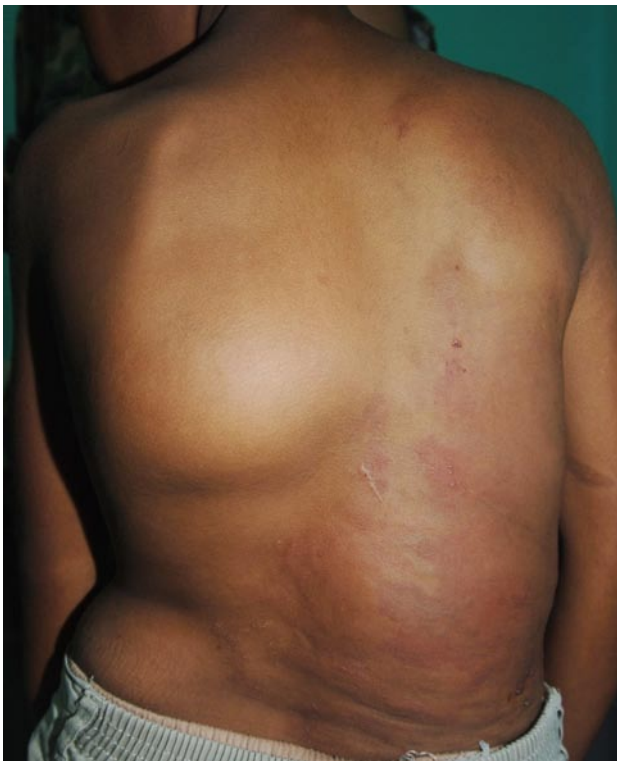

Figure 5. Cervical scoliosis and multiple large subcutaneous lipomas on the back and flank.

Proteus syndrome rather than neurofibromatosis type 1, which previously was believed to be the cause of his deformity.

It has been suggested that Proteus syndrome is caused by a phosphatase and tensin homolog (*PTEN*) mutation; however, the patients cited did not fulfill the current diagnostic criteria that have been established for Proteus syndrome. Subsequently, 34 cases of bona fide Proteus syndrome were studied and none were shown to have a *PTEN* defect.[3] Although the etiology of the condition remains unknown, Happle[4] postulated that Proteus syndrome most likely arises from a postzygotic mutation caused by a dominant lethal gene that survived by mosaicism.

Proteus syndrome is relatively rare, and although there are approximately 250 cases reported in the literature, the actual number of confirmed cases of Proteus syndrome is less than 100 if the current diagnostic criteria are applied. The syndrome can occur in individuals of any race and shows a male predominance, with a male to female ratio of 1.9:1.[5]

Because of the variability in clinical presentation, Proteus syndrome has a high rate of misdiagnosis. Therefore, at the First National Conference on Proteus Syndrome for Parents and Families held at the National Institutes of Health in March 1998, specific diagnostic criteria were established.[6] Regardless of the presence of other clinical findings, the following 3 criteria were believed to be mandatory to make the diagnosis: the lesions must have a mosaic distribution, follow a progressive course, and be inherited in a sporadic fashion.[5,6] In addition to the aforementioned criteria, a patient may have either a connective tissue nevus, with the cerebriform variant being almost pathognomonic (category A); 2 of 3 lesions in category B (epidermal nevus; asymmetric disproportionate tissue overgrowth; or specific tumors before the end of the second decade, namely ovarian cystadenoma, meningioma, testicular tumor, or parotid monomorphic adenoma); or all 3 criteria in category C (dysregulated adipose tissue growth, vascular malformations, or specific facial phenotype).[6] Currently, it is not recommended to combine partial criteria from categories B and C to diagnose Proteus syndrome.[5,6] Other common findings include ophthalmologic abnormalities (42% of patients), central nervous system manifestations inclusive of mental retardation (40% of patients), cystic lung malformations (12%–13% of patients), and urologic abnormalities (9% of patients).[3,5,6] It also is important to be cognizant of the fact that approximately 20% of patients will have premature deaths because of pneumonia, surgical complications, or pulmonary embolism from deep vein thrombosis.[3]

Differential Diagnosis of Proteus Syndrome*[3,6,7]

Syndrome	Mode of Inheritance	Gene Defect	Clinical Characteristics
Proteus (OMIM 176920)	Sporadic, <100 reported cases that meet the diagnostic criteria	Unknown	Connective tissue nevus (cerebriform variant), epidermal nevus, asymmetric disproportionate tissue overgrowth, ovarian cystadenoma, meningioma, testicular tumor, parotid monomorphic adenoma, dysregulated adipose tissue growth, vascular malformations, or specific facial phenotype
Hemihyperplasia/ Multiple lipomatosis[7]	Sporadic, <10 reported cases	Unknown	Moderate asymmetry, overgrowth of the extremities, multiple lipomas that remain stable, possible capillary malformations
Encephalocraniocutaneous lipomatosis (OMIM 176920)	Sporadic, approximately 45 reported cases	Unknown	Primarily involvement of the head and/or neck, with cranial asymmetry and ipsilateral subcutaneous lipomas or connective tissue nevi with overlying areas devoid of hair and associated with neurologic abnormalities
NF-1 (OMIM 162200)	Autosomal-dominant inheritance	NF-1 gene	≥6 café au lait spots, ≥2 neurofibromas of any type, or 1 plexiform neurofibroma; axillary or inguinal freckling; optic pathway gliomas; ≥2 Lisch nodules; and specific bony defect including localized bony hypertrophy
Klippel-Trenaunay-Weber (OMIM 149000)	Sporadic	*VG5Q* (also known as *AGGF1*) gene	Port-wine stain, varicose veins of lower extremities, large hemangioma with associated asymmetric limb hyperplasia +/− macrodactyly
Bannayan-Zonana (OMIM 153480)	Autosomal-dominant inheritance with male predominance	*PTEN* gene	Macrocephaly, developmental delay, hypotonia, subcutaneous and visceral lipomas, lymphangiomas, pigmented macules of the penis

Syndrome	Mode of Inheritance	Gene Defect	Clinical Characteristics
Beckwith-Wiedemann (OMIM 130650)	Autosomal-dominant inheritance with variable expressivity	p57(KIP2) gene (*CDKN1C*) or *NSD1* gene	Exomphalos, macroglossia, hypoglycemia, prenatal and postnatal overgrowth, idiopathic limb hemihypertrophy, increased risk of embryonal cancers

*OMIM indicates Online *Mendelian Inheritance in Man*; NF-1, neurofibromatosis type 1; *VG5Q*, vascular gene on chromosome 5q; *AGGF1*, angiogenic factor with G patch and forkhead-associated domains 1; *PTEN*, phosphatase and tensin homolog; p57, cation independent kinase; KIP2, kinase inhibitor protein; *CDKN1C*, cyclin-dependent kinase inhibitor 1C; *NSD1*, nuclear receptor-binding Su-var, enhancer of Zeste, and trithorax domain protein 1.

When the lesions of Proteus syndrome are fully developed, the diagnosis is not difficult; however, early in childhood, the tissue overgrowth and cutaneous lesions may not be present. One review[5] showed that only 43% (42/97) of patients with Proteus syndrome had vascular malformations or epidermal nevi at birth, but even if present, these findings also can be seen in other syndromes or occur in isolation; consequently, the clinical findings may not be immediately associated with a diagnosis of Proteus syndrome. Furthermore, the characteristic asymmetric disproportionate tissue overgrowth is only seen in 17.5% (17/97) of patients at birth; therefore, diagnosis often is delayed until the lesions are fully expressed later in childhood or adolescence.[3,5]

The most striking feature of Proteus syndrome is asymmetric disproportionate tissue overgrowth with involvement of bones and soft tissues. The overgrowth most often affects an extremity but also commonly involves the skull or vertebrae. The asymmetric bony hyperplasia can result in scoliosis or may be so substantial that bone invades a joint space, resulting in reduced mobility. Characteristically, the overgrowth is progressive, but after adolescence, it tends to plateau.[3] Overgrowth of various organs also can occur, particularly the thymus or spleen; however, it is an uncommon finding.

The most common cutaneous lesions in Proteus syndrome are lipomas, vascular malformations, connective tissue nevi, epidermal nevi, hyperostoses, and focal areas of dermal and/or lipohypoplasia.[3,6,7] The unique combination of tissue overgrowth with focal atrophy results in a body habitus characterized by wasting of the upper body with an elongated thorax and neck and muscular hypertrophy of the lower extremities.

The lipomas in Proteus syndrome can be well-demarcated subcutaneous lesions or locally invasive when located in the intra-abdominal or intrathoracic cavity. Vascular lesions tend to be vascular malformations rather than infantile hemangiomas and can be composed of capillaries, venules, lymphatics, or a combination of these vascular channels. These lesions slowly grow with time in proportion with the patient.

Although connective tissue nevi can occur anywhere on the body, they are almost pathognomonic for Proteus syndrome when they appear on the plantar foot or palmar hand and have a cerebriform appearance. Histologic evaluation of the lesion shows a compact collection of collagen in the dermis that has different staining characteristics from the native collagen. The epidermal nevi in Proteus syndrome are flat and soft rather than verrucous type,[6] and histologically they are characterized by hyperkeratosis, acanthosis, and papillomatosis, without adnexal hyperplasia.

Proteus syndrome has unique findings that help define the condition, but other syndromes can have similar clinical findings. Therefore, it is important to distinguish Proteus syndrome from other overgrowth syndromes (Table).

When confronted with a patient suspected of having Proteus syndrome, the initial evaluation should include baseline skeletal and vertebral radiographs and clinical photographs. In addition, a high-resolution chest computed tomographic scan should be performed to evaluate pulmonary cysts and magnetic resonance imaging to evaluate intracranial malformation and to rule out the presence of intra-abdominal or intrathoracic lipomas.[3,6]

Surgical management should be directed toward functional improvement. Patients with leg-length discrepancy, joint immobility, and macrodactyly are best managed by a team consisting of an experienced orthopedic surgeon, pediatrician, and physical and occupational therapists. The patient also may require consultation with a craniofacial or oral maxillofacial surgeon if airway obstruction or feeding difficulties occur because of hemifacial macrosomia. In addition, surgical consultation may be required for resection of internal lipomas or cystic lung malformations. Because of the high incidence of deep vein thrombosis, it is recommended that antithrombotic prophylaxis is considered prior to all surgical procedures.[3]

Conclusion

Proteus syndrome is a complex disorder with a variable clinical presentation, yet an appropriate diagnosis can be established if the diagnostic guidelines are followed. Despite the rarity of Proteus syndrome, support networks exist to help patients and their families manage the disease.

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