Proteus Syndrome: Case Report and Review

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Abstract
Proteus syndrome (PS) is a rare, progressive hamartomatous disorder characterized by overgrowth and hyperplasia of diverse tissues including connective tissue, bone, skin, adipose, and central nervous system. Mosaic expression of a post-zygotic somatic mutation in the AKT1 gene results in random distribution of affected tissues and creates significant phenotypic variability among patients. Herein, we describe a case of PS presenting with a cerebriform connective-tissue nevus in a 14-year-old male and review the pathogenesis, clinical presentation and differential diagnosis, management, and prognosis of patients with the disorder.

Introduction
Proteus syndrome was first described in 1979 by Cohen and Hayden, and it was named by Weidmann et al. in 1983 for the Greek god Proteus, who was capable of assuming many forms.1,2 With fewer than 100 confirmed cases reported, Proteus syndrome is extremely rare; its estimated incidence is less than 1:1,000,000 persons.3 It is seen twice as frequently in males, and there is no ethnic predilection.4 The variable presentation and rarity of the disease led to frequent misdiagnosis of the disorder until 1999, when Biesecker et al. proposed detailed and specific diagnostic criteria.3

Case Presentation
A 14-year-old Caucasian male presented with a slowly enlarging growth on the bottom of his left foot that was present for about three years. The patient reported some discomfort with ambulation due to the increasing size of the lesion. His medical history included chronic macrocytosis and reticulocytopenia, which prompted a bone marrow biopsy at the age of 10. No evidence of hematologic malignancy was found; however, a non-clonal chromosome 15 deletion: 45 XY del(15)(q11.2) was revealed. (Chromosome 15 deletions have been described in association with myelodysplastic syndrome.) The patient also had a history of developmental abnormalities and was diagnosed with autism/Asperger's disease. An MRI of the brain from five years prior revealed encephalomalacia and periventricular leukomalacia (localized areas of necrosis attributed to infarction or ischemia). One of the patient’s two brothers had spina bifida.

A full skin examination revealed one café au lait macule on the back. The plantar aspect of the left foot contained several flesh-colored cerebriform papules and nodules (Figure 1). Partial biopsy of the lesion was performed. Histology revealed dense connective tissue beneath an acanthotic, acantholytic epidermis. Stellate cells and entrapped adipose tissue were present in the dermis (Figures 2a [2x], 2b [10x]). The patient was assigned a diagnosis of Proteus syndrome and referred for genetic testing.

Pathogenesis
Proteus syndrome is a progressive, hamartomatous disorder that may involve any germ layer. The hypothesized pathogenesis involves a post-zygotic somatic mutation in the AKT1 gene (chromosome 14q32.33), which is lethal in the non-mosaic state.5 This gene belongs to the AKT family of serine/threonine kinases and is involved in regulation of multiple cellular processes, including proliferation and survival, cell size and response to nutrient availability, tissue invasion and angiogenesis.6 Constitutive activation of the protein underlies the overgrowth and tumor susceptibility in patients carrying this mutation. Mosaic expression of the mutation is what results in the random distribution of affected tissue and creates significant phenotypic variability among patients. Accordingly, an early post-zygotic mutation results in a greater number of disease manifestations than a late mutation, because the early somatic cell carrying a mutation would give rise to more affected cell lineages.

Due to the clinical overlap with other hamartomatous disorders, a mutation in the tumor suppressor gene PTEN was initially thought to be pathogenic in PS. However, it is now believed that individuals with PTEN gene mutations and asymmetric overgrowth do not meet the diagnostic criteria for Proteus syndrome. Instead, these individuals are considered part of a larger group of disorders called PTEN hamartoma tumor syndromes. Other entities in this group include Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus-like syndrome.7 AKT1 is activated by loss-of-function mutations in PTEN, which explains why patients with such mutations and those with activating mutations in AKT1 display overlapping clinical features.

Clinical Manifestations
The clinical features of PS arise postnatally with irregular, asymmetric, progressive overgrowth that can involve many tissues, most commonly bone, connective tissue and fat. Skeletal changes include gigantism of the hands and/or feet and partial or complete hemihypertrophy. Localized overgrowths may exert asymmetric forces on the spine and result in scoliosis. Connective-tissue abnormalities, such as cerebriform connective-tissue nevus (CCTN), typically present in the first or second year of life and tend to evolve slowly, in some patients continuing to develop throughout adolescence.8 The lesion is virtually pathognomonic for PS and appears as gyriform gross thickenings of cutaneous and subcutaneous tissues, most commonly on the soles and occasionally on the hands, abdomen, and nose.

Other dermatological manifestations include linear verrucous epidermal nevus, which tend to develop in the first year of life, and vascular malformations that can be either venous, capillary, lymphatic-type, or mixed.9 Four types of abnormalities of fat may occur in Proteus syndrome: (1) lipomas, (2) lipohypoplasia, (3) fatty overgrowth, and (4) localized fat deposits or partial lipohypoplasia. Lipomas may be single or multiple and occur subcutaneously or internally. Lipomas of the abdomen and thorax can be very aggressive despite their benign histology.5,9 Specific facial features have been described in
Table 1. Proteus Syndrome Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criteria Category (Diagnosis requires either A, two from B, or three from C)</th>
<th>Clinical Characteristics</th>
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<tbody>
<tr>
<td>Category A</td>
<td>Cerebriform connective tissue nevus</td>
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<tr>
<td>Category B</td>
<td>1. Linear epidermal nevus</td>
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<td></td>
<td>2. Asymmetric, disproportionate overgrowth with at least one of the following:</td>
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<tr>
<td></td>
<td>· Affected limbs</td>
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<tr>
<td></td>
<td>· Hypoplasia of the skull</td>
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<td></td>
<td>· Hypoplasia of the external auditory canal</td>
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<td></td>
<td>· Megaspongydylodysplasia</td>
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<td></td>
<td>· Viscera: spleen or thymus</td>
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<tr>
<td>Category C</td>
<td>3. Specific tumors before the second decade:</td>
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<tr>
<td></td>
<td>· Bilateral ovarian cystadenoma</td>
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<tr>
<td></td>
<td>· Parotid monomorphic adenoma</td>
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</table>

Patients with PS and are most commonly seen in individuals with cognitive deficits. These include down-sloping palpebral fissures, flattening of the malar bones, a relative lengthening of the face, low nasal bridge with wide nostrils, and a persistently open mouth. Our patient did not display any of these characteristics.

Central nervous system abnormalities are seen in up to 40% of patients with PS. Dietrich et al. described 12 children with PS whose CNS abnormalities included hemimegalencephaly (8%), hypodense periventricular white matter (4%), periventricular calcification (3%), corpus callosal abnormalities (3%), atrophic brains (2%), and Dandy-Walker malformation (1%). Mental deficiency is seen in approximately 30% of cases.

While no specific hematologic abnormalities have been described in association with PS, studies have demonstrated that AKT1 and AKT2 are critical regulators of long-term hematopoietic stem-cell function. It is feasible that an AKT1 gene mutation may underlie the chronic macrocytosis and reticulocytopenia observed in our patient.

Patients with PS are prone to developing several types of tumors, most commonly monomorphic adenomas of the parotid gland, ovarian cystadenomas, meningiomas, and various types of testicular tumors. Cystic lung disease may cause pulmonary insufficiency, persistent atelectasis, pneumonia, or even death. Other manifestations include ophthalmologic findings such as strabismus, epibulbar cysts, and epibulbar dermoids (42%); otolaryngologic abnormalities (37%); mental deficiency (30%); non-cystic pulmonary disease (20%); dental abnormalities (19%); reproductive/genital non-tumor abnormalities (18%); male reproductive tumors (11%) and renal/urologic manifestations (9%); and hair and nail abnormalities.

Diagnosis
The diagnosis of Proteus syndrome is based on clinical findings. Individuals must meet all of the general criteria, including mosaic distribution of lesions, sporadic occurrence, and progressive course, along with certain specific criteria as outlined in Table 1. Although PS is primarily a clinical diagnosis, molecular genetic testing for the somatic mutation in the AKT1 gene can be helpful to confirm the diagnosis. This can be technically challenging because blood is not an appropriate source and tissue may show low-level mosaicism. Skin scrapings from epidermal nevi in PS patients have been shown to be a good source of mutant cells and may provide an alternate source for genetic testing. It is important to note that PS is not inherited, so prenatal testing is not indicated.

Differential Diagnosis
Among the differential diagnoses for Proteus syndrome are those entities described as part of PTEN hamartoma tumor syndrome. Bannayan-Riley-Ruvalcaba syndrome is an autosomal-dominant disorder characterized by macrocephaly, angiomatosis, lipomatosis, polyposis of the colon and rectum, and pigmented macules of the penis. These patients lack the progressive digital overgrowth, skull exostoses, epidermal nevi, and palmar or plantar changes seen in Proteus syndrome. Patients with Cowden syndrome typically present with facial trichilemmomas, acral keratoses, papillomatous lesions, lipomas, hemangiomas, and epidermal nevi (Cowden nevus), but do not develop cerebriform connective-tissue nevi. These patients also carry an increased risk for breast, thyroid, and endometrial cancers. Patients with Proteus-like syndrome have significant clinical features of PS but do not meet the diagnostic criteria for PS. They are distinguished by macrocephaly, marked lipohypertrophy, and lack of progressive bony overgrowth.

In SOLAMEN (segmental overgrowth, lipomatosis, AVMs, epidermal nevus) syndrome, patients display thickening of the soles and increased wrinkling instead of the gyri found in CCTN. There is segmental proportionate overgrowth with soft-tissue hypertrophy and ballooning effect, as well as lymphatic and shunting arteriovenous malformations. Proteus syndrome may be distinguished from neurofiromatosis by the absence of multiple café au lait macules, Lisch nodules, axillary freckling, and multiple neurofibromas. Hemihyperplasia and multiple lipomatosis syndrome (HHML) is characterized by subcutaneous lipomatosis and asymmetric overgrowth (hemihyperplasia) that is not as progressive as in PS. Syndromes characterized by vascular malformations may also be considered in the differential diagnosis of PS. In Maffucci syndrome, enchondromatosis, most commonly of the hands and feet, with multiple cavernous hemangiomas are seen. This should not be difficult to distinguish from Proteus syndrome owing to the lack of enchondromatosis in Proteus syndrome. Klippel-Trenaunay syndrome is characterized by the three main features of nevus flammeus (port-wine stain), venous and lymphatic malformations, and soft-tissue hypertrophy of the affected limb. There are no CCTN seen, and overgrowth is present at birth and more severe than in PS. In Parkes Weber, a mutation in the RASA1 gene leads to multiple capillary malformations, including AV fistulas that can lead to heart failure, as well as overgrowth of one limb, most commonly the leg. In the differential diagnosis of the CCTN is isolated plantar collagenoma, a hamartomatous lesion consisting of proliferation of normal collagen tissue. Collagenomas are commonly encountered in other genetic disorders, such as Buschke-Ollendorff syndrome, a rare autosomal-dominant condition, resulting from nonsense mutation in the LEMD3 gene, which encodes for a potent negative regulator of bone morphogenetic protein and transforming growth factor-β signaling pathways. Recently,
Histopathology
Histopathologically, cerebriform connective-tissue nevi are characterized by an irregular proliferation of highly collagenized fibrous tissue. Biopsies of lipomatous overgrowths reveal nonencapsulated lobules and mature adipocytes. Vascular malformations are lined by flat endothelium, exhibiting a normal, slow rate of turnover. The flat, organoid type of epidermal nevus in PS shows acanthosis, hyperkeratosis, and increased thickness, and development of new lesions. Lesions increased in size and/or number in 8 out of 10 children. Epidermal nevi and vascular malformations generally did not spread or increase in number.

Other imaging recommendations include intracranial MRI to evaluate for CNS malformations that may be associated with developmental delay, mental retardation or seizures. Findings may include multiple meningiomas, polymicrogyria, and periventricular heterotopias. Abdominal MRI is recommended to exclude intra-abdominal lipomas, regardless of the presence of symptoms, due to the aggressive nature of these lesions. CT of the chest to evaluate pulmonary cystic malformations should be carried out if clinically warranted to evaluate for cystic malformations.

Cerebriform connective-tissue nevus (CCTN) is a common dermatologic overgrowth that is usually found at the plantar aspect of the foot. The grooves in CCTN can be difficult to clean, leading to the accumulation of bacteria and fungus that may cause infection and a malodor. CCTN can progressively increase in size, grow on previously non-involved areas of the foot and coalesce. This can be disfiguring, painful, and interfere with ambulation. Surgical removal of CCTN can lead to disappointing results since recurrence and painful scarrring is possible. Dermatological follow-ups and the use of custom orthotics to manage pain, pressure ulcerations, and/or skin breakdown are preferred treatments. Because patients and their families can undergo a great deal of stress from this disease, clinicians are encouraged to assess psychosocial issues routinely with parents and children and refer for counseling and peer-support groups if needed.

Prognosis
Regarding progression of skin lesions, Beachkofsky et al. evaluated 36 patients with Proteus syndrome with serial photography for an average of 53 months. Cerebriform connective-tissue nevus showed progression in 13 children but not in 3 adults. Lesions progressed by expansion into previously uninvolved skin, increased thickness, and development of new lesions. Lipomas increased in size and/or number in 8 out of 10 children. Epidermal nevi and vascular malformations generally did not spread or increase in number.

Long-term prognosis varies across patients. Approximately 20% of PS patients suffer premature death, most commonly due to venous or pulmonary thromboembolism, pneumonia, or surgical complications.

Conclusion
Proteus syndrome is a complex disease that can involve many areas of the body, especially the skeletal system, connective tissue, fat, and central nervous system. The variable clinical presentation, rarity of the disorder, and clinical overlap with several other diseases has led to significant confusion and misdiagnosis. Molecular genetic testing can be performed, with the highest yield from epidermal nevi or tissue specimens. Patients should be managed with a multidisciplinary approach.

References

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